



Europäisches Patentamt

⑯

European Patent Office

Office européen des brevets

⑯ Publication number:

0 232 740
A1

⑯

EUROPEAN PATENT APPLICATION

⑯ Application number: 87100448.7

⑯ Date of filing: 15.01.87

⑯ Int. Cl. 4: C 07 D 277/68, C 07 D 209/38,
C 07 D 209/40, C 07 D 263/58,
C 07 D 277/82, C 07 D 417/06,
A 61 K 31/495, C 07 D 513/04
// (C07D513/04, 277:00, 221:00)

⑯ Priority: 17.01.86 GB 8601160

⑯ Date of publication of application: 19.08.87
Bulletin 87/34

⑯ Designated Contracting States: AT BE CH DE ES FR GB
GR IT LI LU NL SE

⑯ Applicant: Fujisawa Pharmaceutical Co., Ltd., 3,
Doshomachi 4-chome Higashi-ku, Osaka-shi,
Osaka 541 (JP)

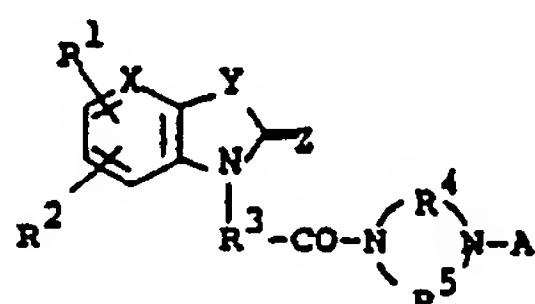
⑯ Inventor: Ueda, Ikuo, 2-11-95, Uenohigashi,
Toyonaka-shi Osaka (JP)
Inventor: Matsuo, Masaaki, No. 5-2-1-619,
Nakasakurazuka, Toyonaka-shi Osaka (JP)
Inventor: Tsuji, Kiyoshi, No. 170, Hatacho, Kishiwada-shi
Osaka (JP)
Inventor: Okumura, Hiroyuki, No. 3-19-3, Nishifukui,
Ibaraki-shi Osaka (JP)
Inventor: Nakaguchi, Osamu, No. 1-15-34,
Nakasakurazuka, Toyonaka-shi Osaka (JP)

⑯ Representative: Türk, Gille, Hrabal, Bruckner Strasse 20,
D-4000 Düsseldorf 13 (DE)

⑯ N-containing fused heterocyclic compounds, processes for the preparation thereof and pharmaceutical composition comprising the same.

⑯ A compound of the formula:

or a group of the formula: $-N=R^8$, pharmaceutically acceptable salts thereof, processes for the preparation thereof, pharmaceutical compositions comprising the same and their use as pharmaceuticals.



EP 0 232 740 A1

wherein

R¹ and R² are each hydrogen, halogen, aryl, lower alkyl, halo(lower)alkyl or nitro,

R³ is lower alkylene,

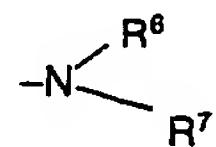
R⁴ and R⁵ are each lower alkylene,

X is CH or N,

Y is S, O, NH, C=N-OH or CO,

Z is O or NH, and

A is hydrogen, nitroso, amidino, a group of the formula:



N-CONTAINING FUSED HETEROCYCLIC COMPOUNDS,
PROCESSES FOR THE PREPARATION THEREOF AND
PHARMACEUTICAL COMPOSITION COMPRISING THE SAME

This invention relates to new N-containing fused heterocyclic compounds. More particularly, this invention relates to new N-containing fused heterocyclic compounds and pharmaceutically acceptable salts thereof which have pharmacological activities, processes for preparation thereof, a pharmaceutical composition comprising the same and method of use thereof.

5 Accordingly, one object of this invention is to provide the new and useful N-containing fused heterocyclic compounds and pharmaceutically acceptable salts thereof.

10 Another object of this invention is to provide processes for preparation of the N-containing fused heterocyclic compounds and pharmaceutically acceptable salts thereof.

15 A further object of this invention is to provide a pharmaceutical composition comprising said N-containing fused heterocyclic compounds or a pharmaceutically acceptable salt thereof.

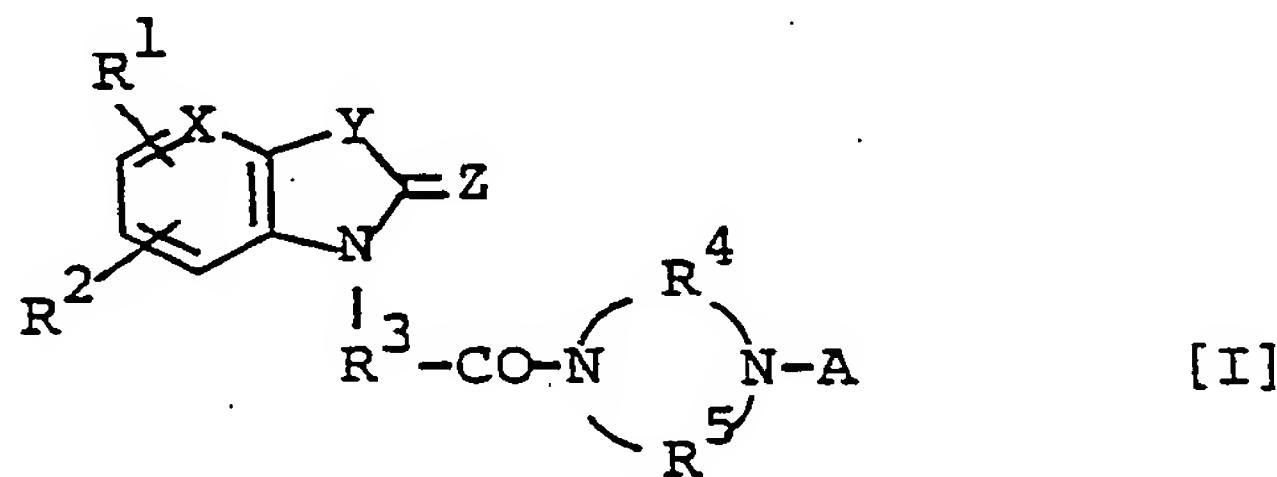
Still further object of this invention is to provide a method of using said N-containing fused heterocyclic compounds or a pharmaceutically acceptable salt thereof for therapeutic treatment of thrombosis, inflammation, 5 or allergic disease, or as analgesic of human being and animals.

With regard to the state of the art in this field, 5-chloro-3-{[4-(2-hydroxyethyl)-1-piperazinyl]carbonylmethyl}-2-benzothiazolinone hydrochloride (generic name : 10 Tiaramide hydrochloride) has been well known as anti-inflammatory drug.

The antithrombotic activity of said compound has also been known as described in The Japanese Journal of Pharmacology [Volume 30, Page 905-912, (1980)].

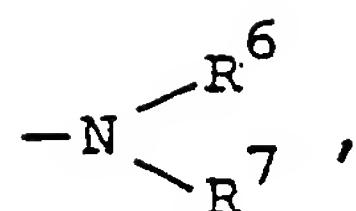
15 The object N-containing fused heterocyclic compounds of this invention are novel and represented by the following general formula [I] :

20



25 wherein R^1 and R^2 are each hydrogen, halogen, aryl, lower alkyl, halo(lower)alkyl or nitro, R^3 is lower alkylene, R^4 and R^5 are each lower alkylene, X is CH or N, Y is S, O, NH, C=N-OH or CO, Z is O or NH, and A is hydrogen, nitroso, amidino, a group of the formula:

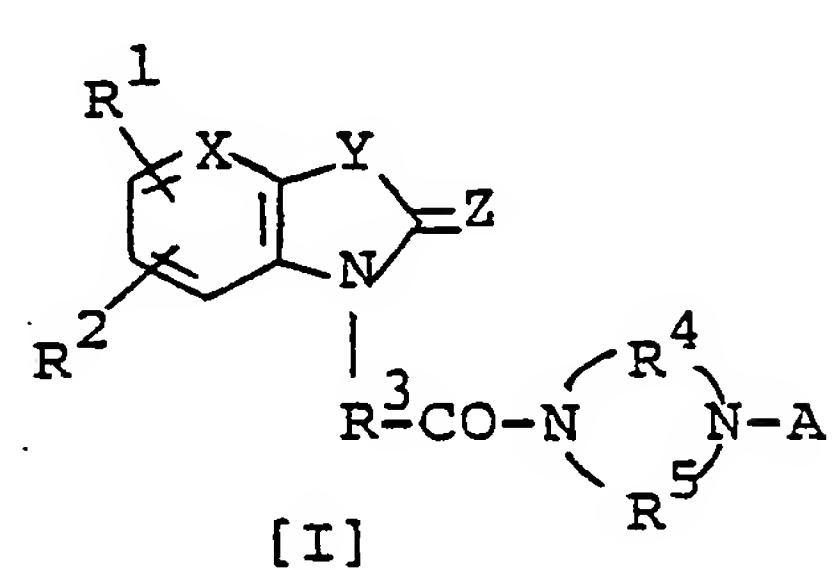
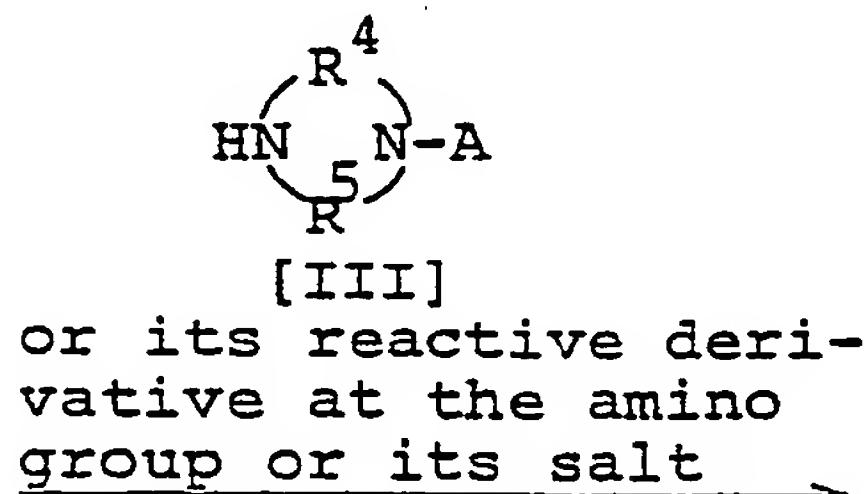
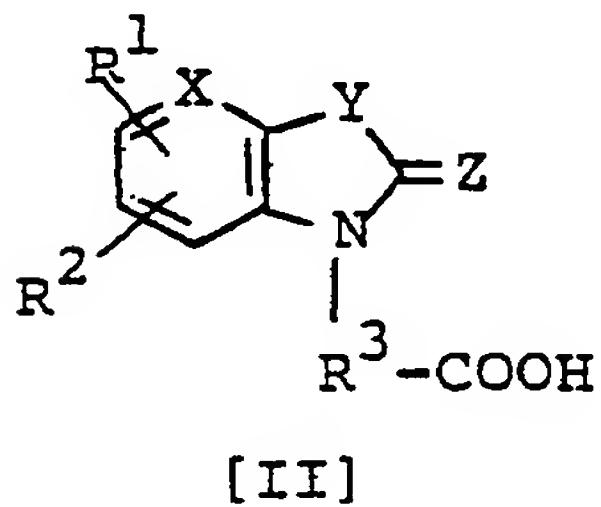
30



wherein R⁶ and R⁷ are each hydrogen, lower alkyl, acyl, or lower alkaneimidoyl which may be substituted with esterified carboxy, or
5
a group of the formula: -N=R⁸
wherein R⁸ is lower alkylidene which may be sub-
10
stituted with aryl optionally sub-
stituted with suitable substituent(s).

15 The object compound [I] of the present invention can be prepared by the following processes.

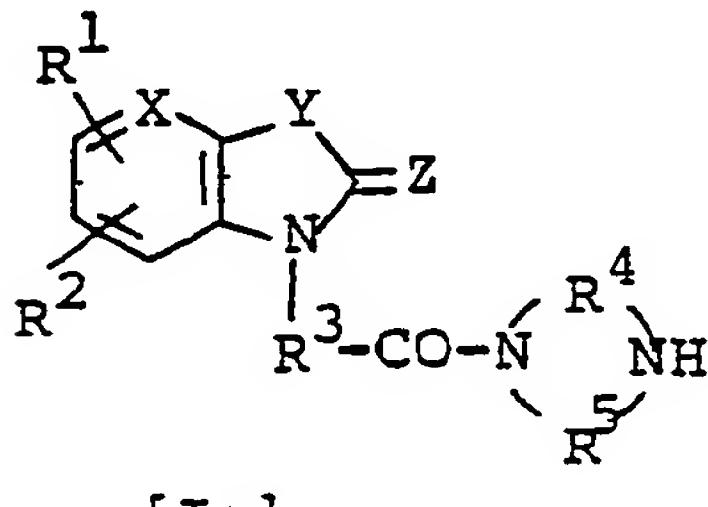
Process 1



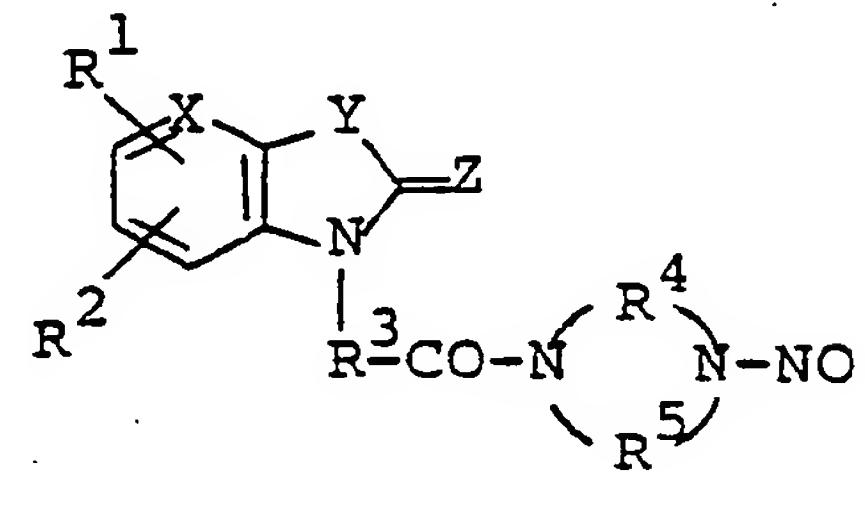
25 or its reactive derivative at the carboxy group or its salt

or its salt

Process 2



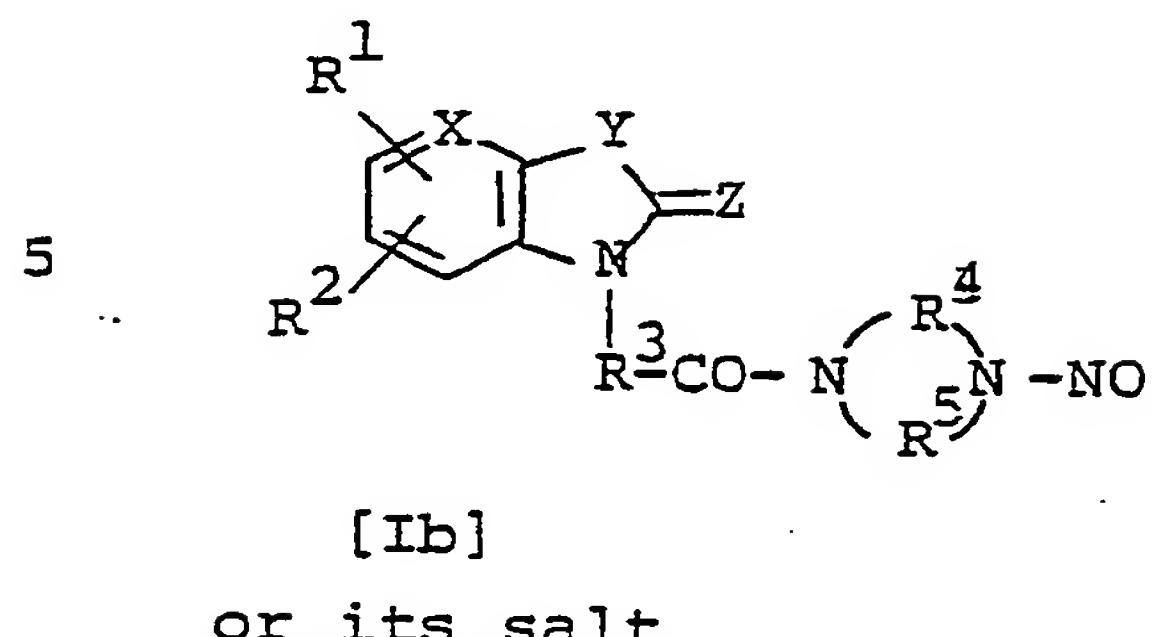
30 Nitrosation



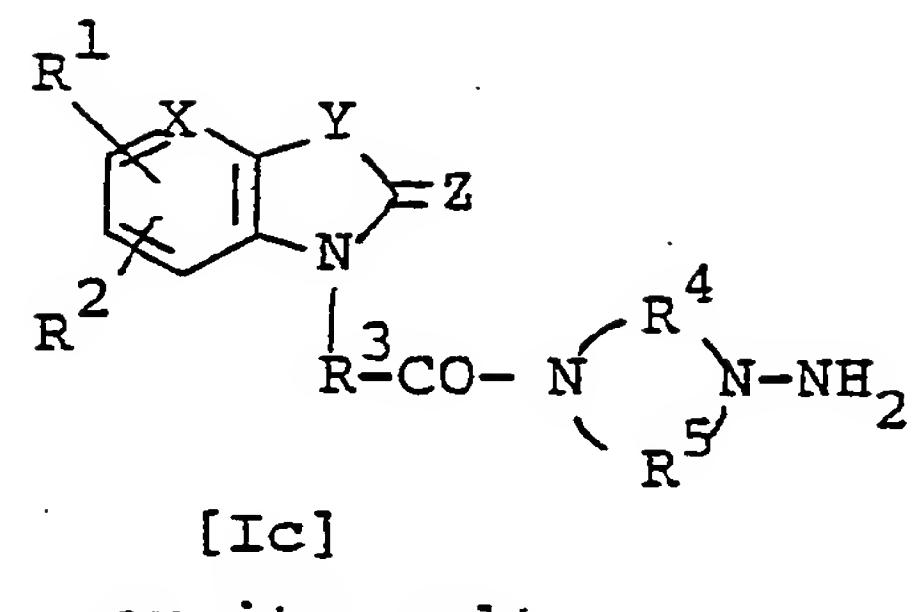
35 or its salt

or its salt

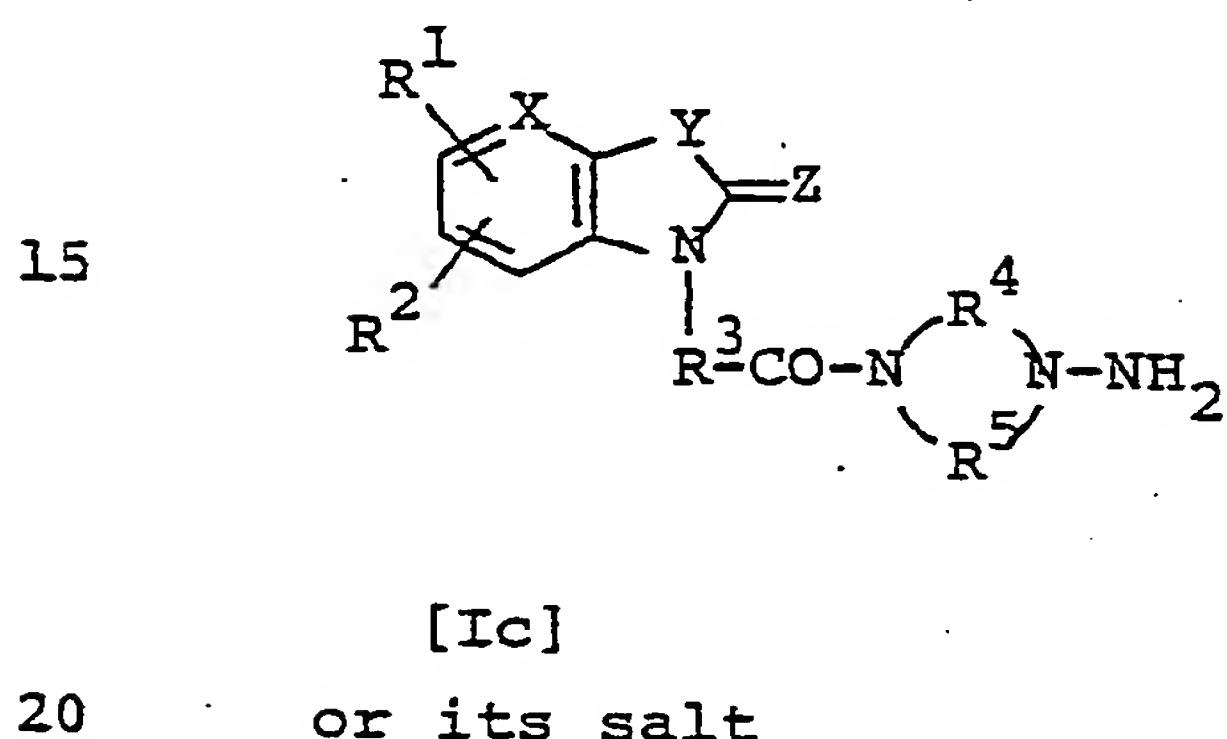
Process 3



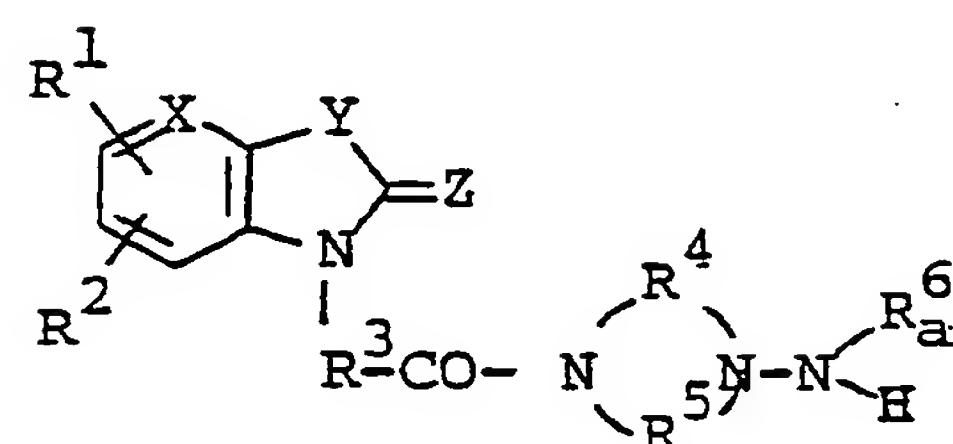
reduction



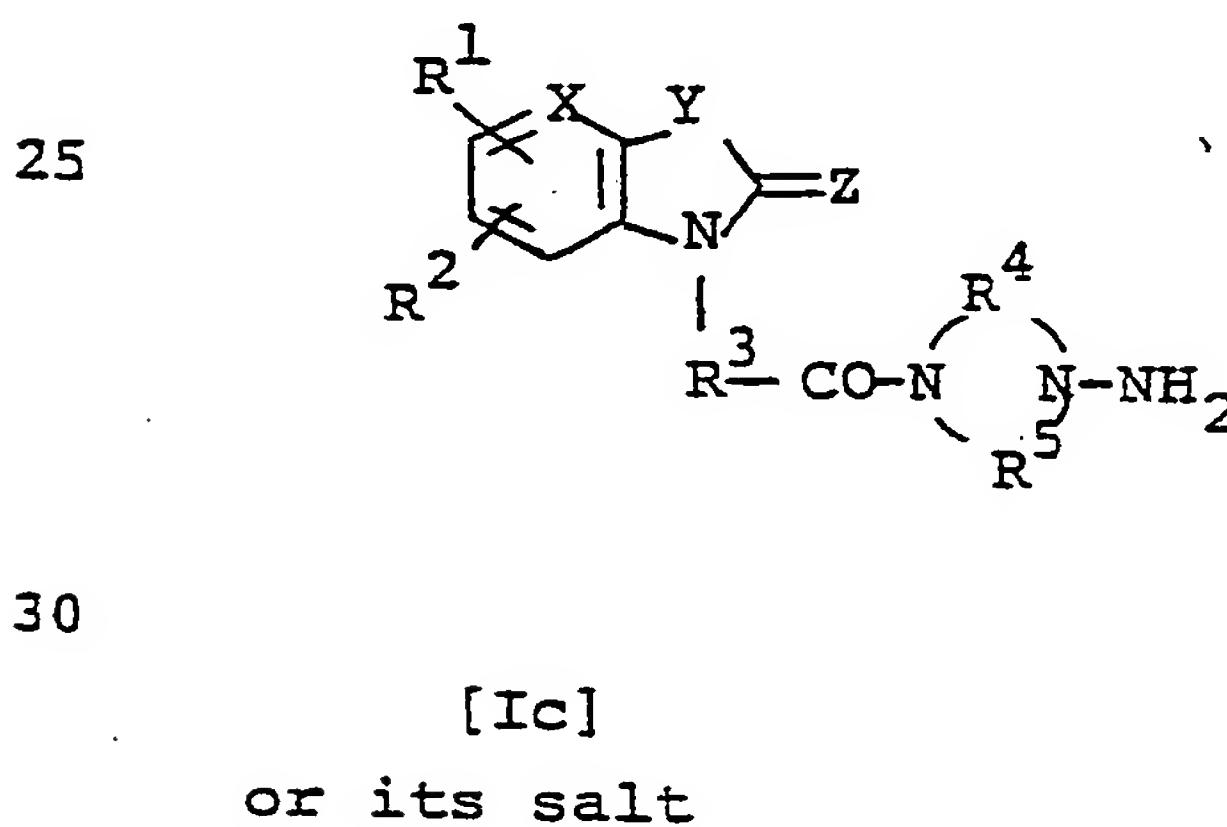
Process 4



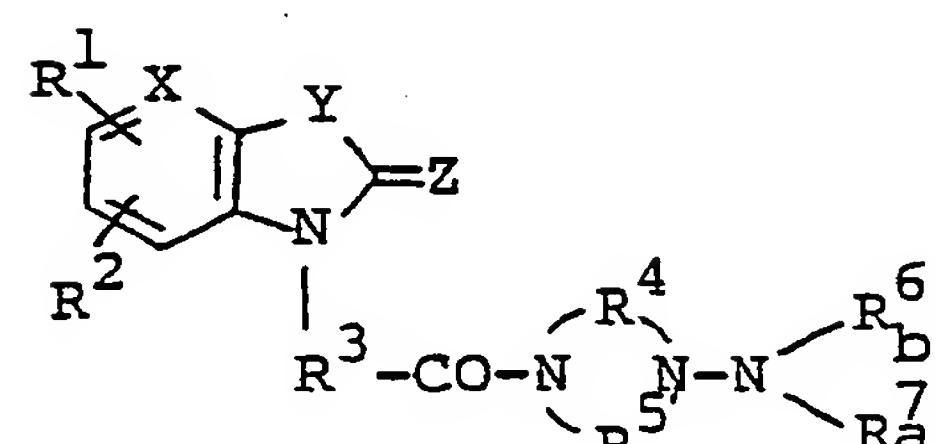
acylation



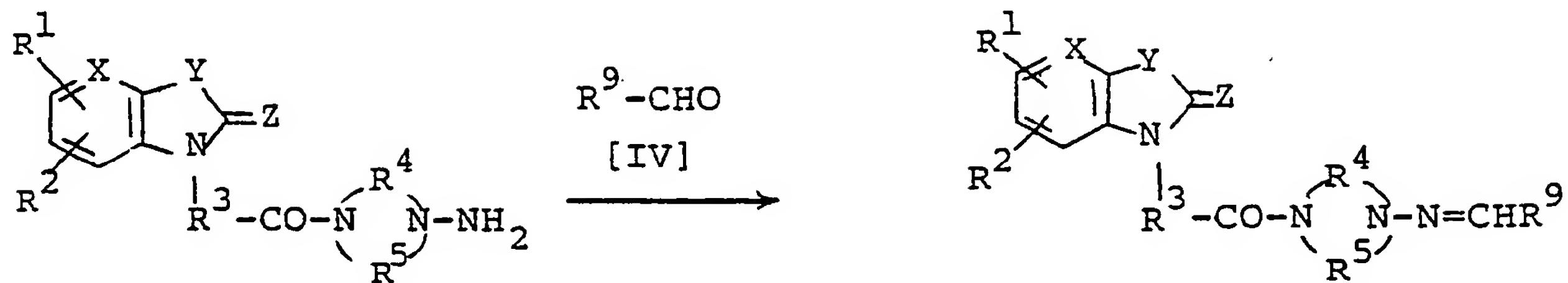
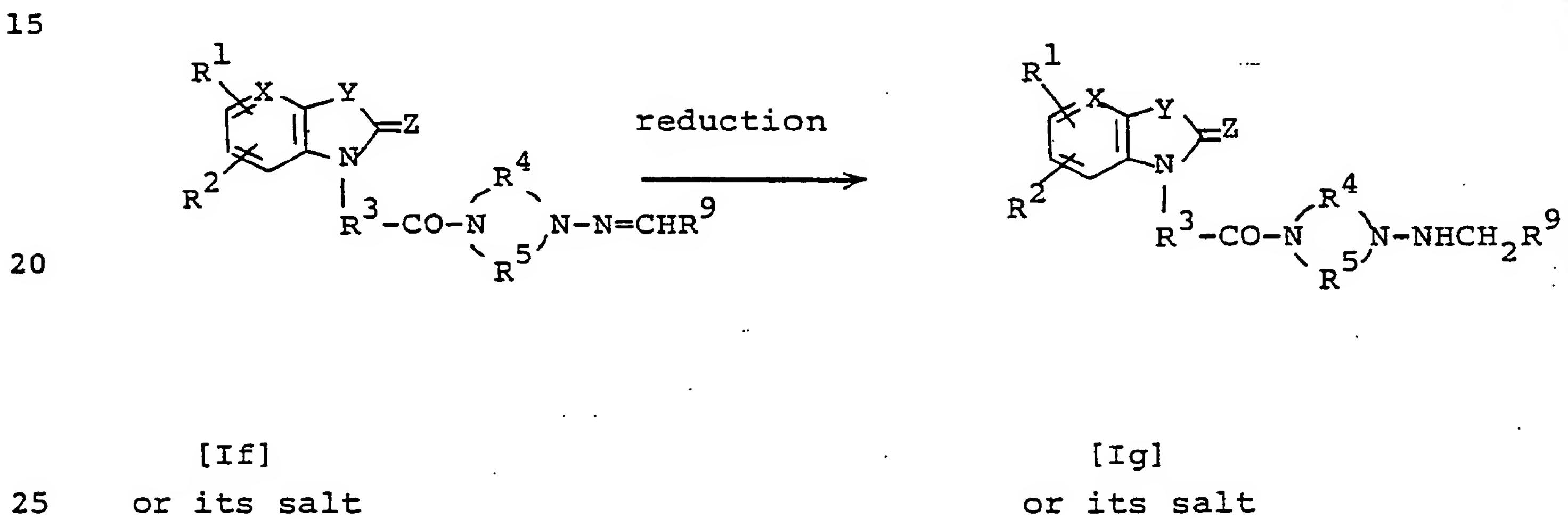
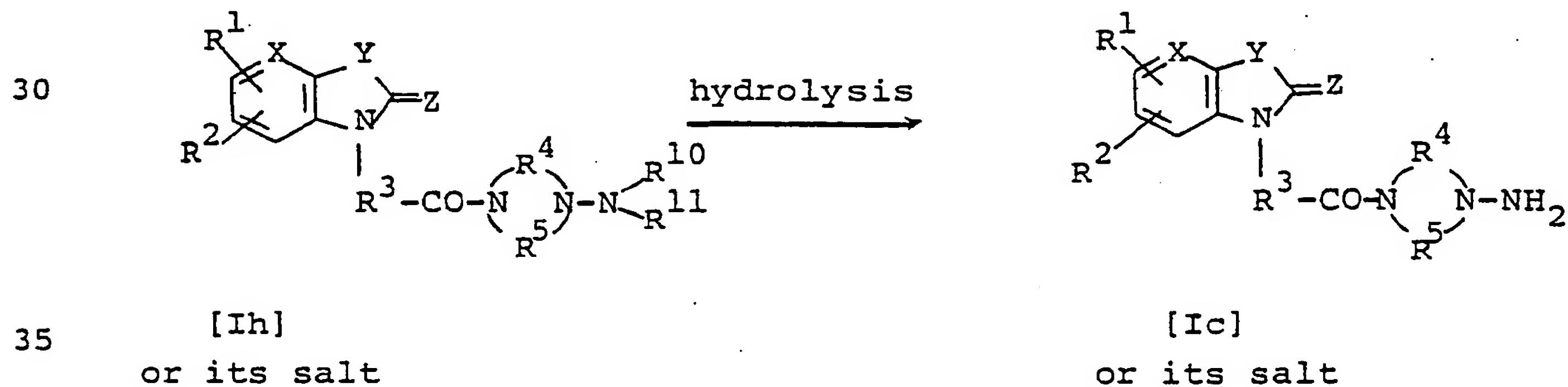
Process 5



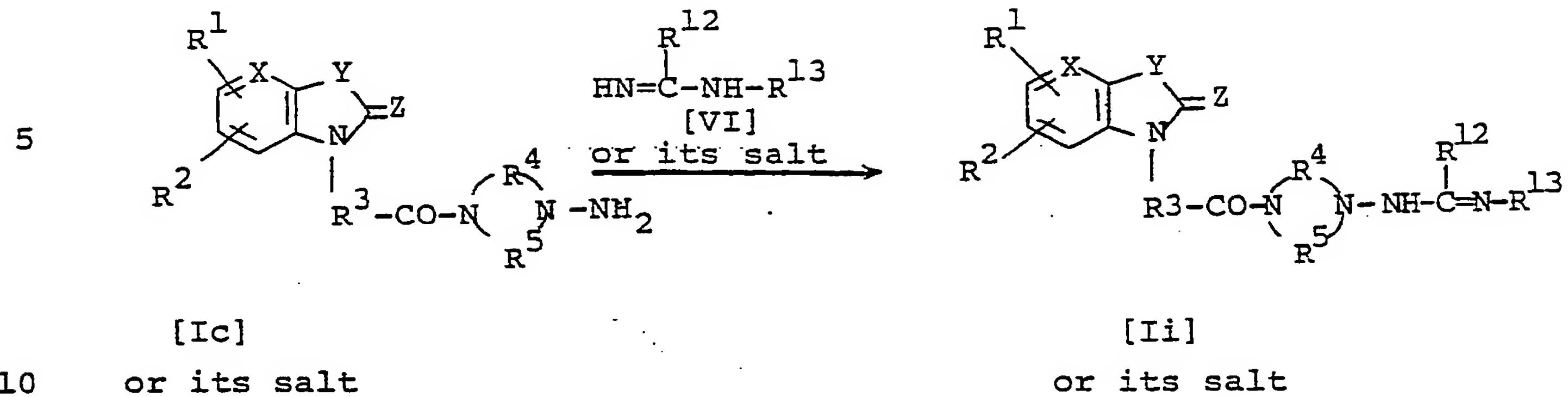
alkylation



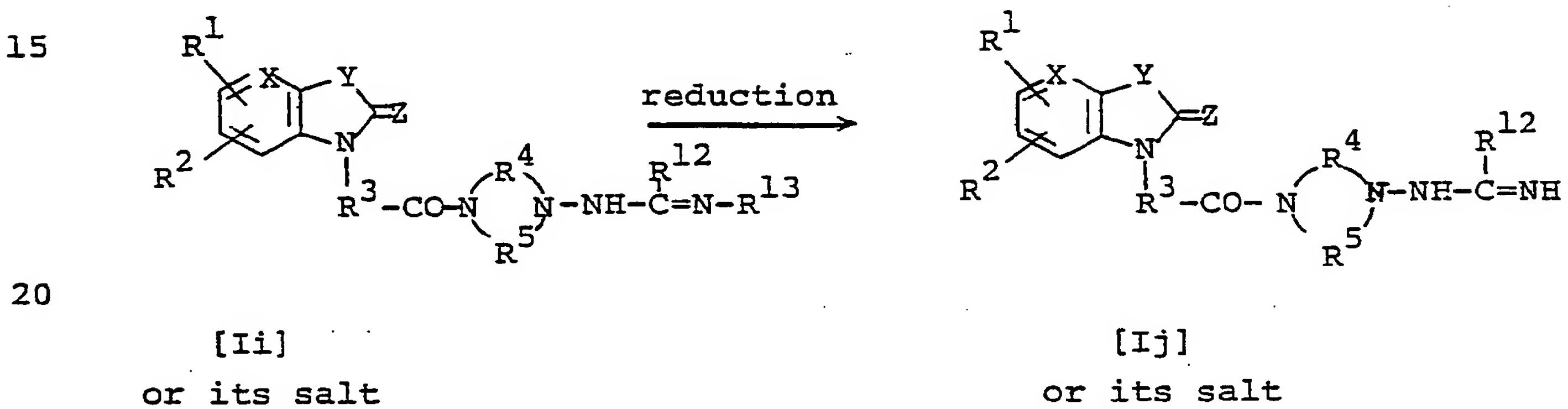
35

Process 6Process 7Process 8

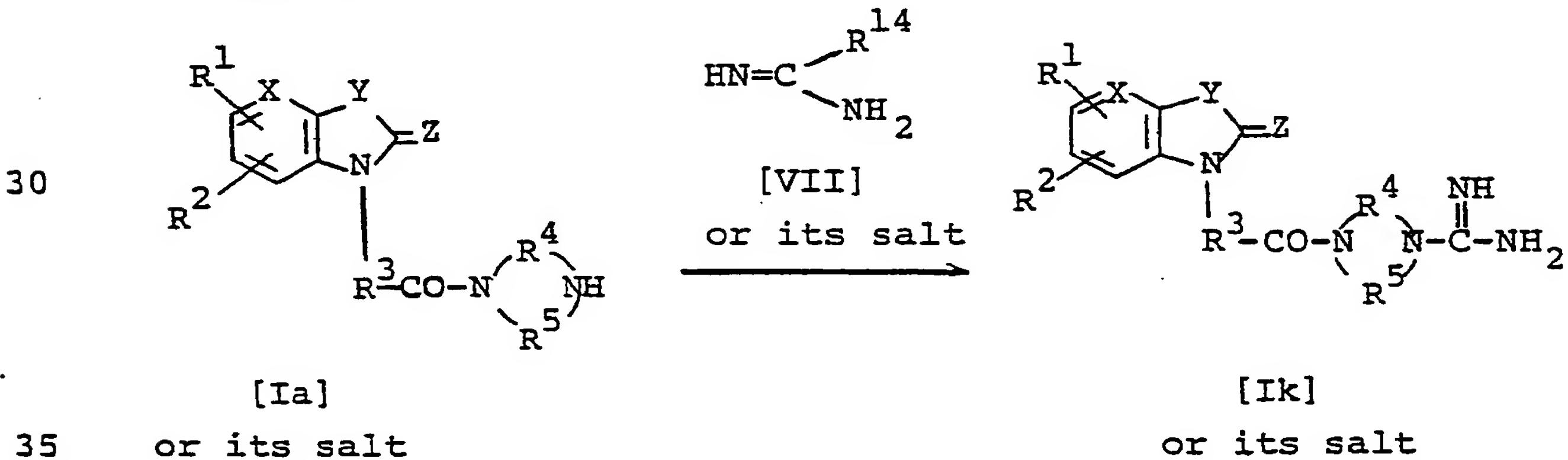
Process 9



Process 10



Process 11



wherein R^1 , R^2 , R^3 , R^4 , R^5 , X , Y , Z and A are each as defined above,

R_a^6 is acyl,

R_b^6 is lower alkyl,

R_a^7 is hydrogen or lower alkyl,

R^9 is hydrogen, lower alkyl or aryl optionally substituted with suitable substituent(s),

R^{10} is acyl and R^{11} is hydrogen or R^{10} and R^{11} are combined together to form a group of the formula : $=R^8$ wherein R^8 is as defined above,

R^{12} is lower alkyl,

R^{13} is esterified carboxy and

R^{14} is lower alkylthio.

In the above and subsequent description of the present specification, suitable examples and illustrations for the various definitions to be included within the scope of the invention are explained in detail as follows:

The term "lower" is intended to mean 1 to 6 carbon atom(s) unless otherwise indicated.

Suitable examples of the lower alkyl may be a straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl or the like.

Suitable example of "lower alkyl" moiety in the term "halo(lower)alkyl" and "lower alkylthio" can be referred to the ones as exemplified above.

Suitable example of "halo(lower)alkyl" may include "monohalo(lower)alkyl" [e.g. chloromethyl, bromomethyl, fluoromethyl, etc.], "dihalo(lower)alkyl" [e.g. dichloromethyl, dibromomethyl, difluoromethyl, etc.] and "trihalo(lower)alkyl" [e.g. trichloromethyl, tribromomethyl, trifluoromethyl, trifluoroethyl, etc.] and the like.

Suitable examples of "lower alkoxy" may include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentyloxy, hexyloxy and the like.

5 Suitable examples of "halogen" may include chlorine, bromine, iodine and fluorine.

Suitable examples of "aryl" may include phenyl, tolyl, xylol, cumenyl, naphtyl, and the like.

10 Suitable examples of "suitable substituent(s)" on said aryl may include hydroxy and the like, the number of which may be one or more.

15 Suitable examples of the lower alkylene group may be a straight or branched one such as methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, propylene, methylethylene, ethylethylene, propylethylene, isopropylethylene, methylpentamethylene or the like.

20 Suitable examples of the lower alkylidene group may include methylene, ethylidene, propylidene, isopropylidene, butylidene, sec-butylidene, isobutylidene, hexylidene, isohexylidene and the like.

25 Suitable examples of acyl may include lower alkanoyl [e.g. formyl, acetyl, propionyl, valeryl, pivaloyl, etc.], lower alkoxy carbonyl [e.g. methoxycarbonyl, ethoxy carbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, t-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, etc.],

30 lower alkanesulfonyl [e.g. methanesulfonyl, ethanesulfonyl, propanesulfonyl, butanesulfonyl, pentanesulfonyl, hexanesulfonyl, etc.], aroyl [e.g. benzoyl, naphthoyl, etc.] which may be substituted with halogen as exemplified above, arylcarbamoyl [e.g. phenylcarbamoyl, tolylcarbamoyl, etc.] which may be substituted with halogen as mentioned above, and the like.

35 Suitable esterified carbóxy may include lower alkoxy carbonyl

(e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert-butoxycarbonyl, etc.), mono(or di or tri)phenyl(lower)alkoxycarbonyl which may have a nitro group (e.g. benzyloxycarbonyl, 5 p-nitrobenzyloxycarbonyl, phenethyloxycarbonyl, benzhydryloxycarbonyl, trityloxycarbonyl, etc.), and the like.

Suitable examples of "lower alkaneimidoyl" may include acetimidoyl, propioimidoyl, etc.

10 Suitable pharmaceutically acceptable salts of the object compound [I] are conventional non-toxic salts and include an organic acid salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate,

15

(continued to the next page)

20

25

30

35

benzenesulfonate, toluenesulfonate, etc.], an inorganic acid salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.], a salt with an amino acid [e.g. arginine salt, ornithine salt, etc.], and the like.

5 In this respect, it is to be noted that the compounds [Ia] to [Ik] are included within the scope of the compound [I], and accordingly the suitable salts of these compounds [Ia] to [Ik] are to be referred to those as exemplified for the object compound [I] in
10 the above.

15 The processes for preparing the object compound [I] and salts thereof are explained in detail in the following.

15 Process 1

20 The object compound [I] or its salt can be prepared by reacting the compound [II] or its reactive derivative at the carboxy group or its salt with the compound [III] or its reactive derivative at the amino group or its salt.

25 Suitable reactive derivative at the carboxy group of the compound [II] may include an acid halide, an acid anhydride, an activated amide, an activated ester and the like.

30 Suitable examples of such reactive derivatives may be acid chloride, an acid azide, a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, etc.], aliphatic carboxylic acid [e.g. pivalic acid, acetic acid, trichloroacetic acid, etc.] or the like, a symmetrical acid anhydride, an activated amide with imidazole, triazole or dimethylpyrazole, an activated ester with N-hydroxysuccinimide, N-hydroxyphthalimide or 1-hydroxy-6-chlorobenzotriazole, and the like.

Suitable reactive derivatives at the amino group of the compound [III] include conventional ones used in amidation, for example, Schiff's base type imino or its tautomeric enamine type isomer formed by reaction of the compound [III] with a carbonyl compound, a silyl derivative formed by reaction of the compound [III] with a silyl compound such as trimethylsilylacetamide, bis(trimethylsilyl)acetamide or the like, a derivative formed by reaction of the compound [III] with phosphorus trichloride or phosgene, and the like.

This reaction may be carried out in the presence of a conventional condensing agent such as N,N-dicyclohexylcarbodiimide; phosphorus oxychloride; phosphorus trichloride; phosphorus pentachloride; thionyl chloride; oxalyl chloride; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent, for example (chloromethylene) dimethylammonium chloride produced by the reaction of dimethylformamide with thionyl chloride or phosgene, a compound produced by the reaction of dimethylformamide with phosphorus oxychloride, etc.; or the like.

This reaction is usually carried out in a conventional solvent such as water, methanol, ethanol, propanol, tetralin, tetrahydrofuran, dioxane, chloroform, toluene, dimethylformamide, dimethylsulfoxide, methylene chloride or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction is usually carried out under cooling, at ambient temperature or under warming.

Process 2

The object compound [Ib] or its salt can be prepared

by subjecting the compound [Ia] or its salt to nitrosation reaction.

The reaction can be carried out by reacting the compound [Ia] or its salt with nitrosating agent.

5 Suitable nitrosating agent used in the present reaction may include nitrite compound [e.g. isoamyl nitrite, sodium nitrite, etc.] and the like.

10 This reaction is usually carried out in a conventional solvent such as methanol, ethanol, tetrahydrofuran, dioxane, methylene chloride, chloroform, benzene, dimethylformamide, dimethyl sulfoxide or any other organic solvent which does not adversely influence the reaction.

15 The reaction temperature is not critical, and the reaction can be carried out under cooling to warming.

Process 3

The object compound [Ic] or its salt can be prepared by reducing the compound [Ib] or its salt.

20 The reaction including chemical reduction and catalytic reduction, may be carried out in a conventional manner.

25 Suitable reducing agents to be used in chemical reduction are a metal [e.g. tin, zinc, iron, etc.], a combination of such metal and/or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.],
30 a metal hydride compound such as aluminum hydride compound [e.g. lithium aluminum hydride, sodium aluminum hydride, aluminum hydride, lithium trimethoxyaluminum hydride, lithium tri-t-butoxyaluminum hydride, etc.], borohydride compound [e.g. sodium borohydride, lithium borohydride, sodium cyanoborohydride, tetramethylammonium
35

borohydride, borane, diborane, etc.], a phosphorus compound [e.g. phosphorus trichloride, phosphorus tribromide, triphenylphosphine, triethylphosphine, etc.] and the like.

5 Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalyst [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalyst [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.], nickel catalyst [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalyst [e.g. reduced cobalt, Raney cobalt, etc.], iron catalyst [e.g. reduced iron, Raney iron, etc.], copper catalyst [e.g. reduced copper, Raney copper, Ullman copper, etc.], or the like.

20 The reduction is usually carried out in a solvent. A suitable solvent to be used may be water, alcohol [e.g. methanol, ethanol, propanol, etc.], acetonitrile or any other conventional organic solvent such as diethyl ether, dioxane, tetrahydrofuran, etc. or a mixture thereof. Additionally, the aforementioned liquid acids to be used in chemical reduction can also be used as a solvent.

25 The reaction is preferably carried out under cooling to warming.

Process 4

30 The object compound [Id] or its salt can be prepared by acylating a compound [Ic] or its salt.

35 Suitable acylating agent to be used in this reaction includes an organic acid such as alkanoic acid [e.g. formic acid, acetic acid, propionic acid, etc.], arencarboxylic acid (e.g. benzoic acid, toluenecarboxylic acid, etc.) which may have halogen, lower alkanesulfonic

acid [e.g. methanesulfonic acid, etc.], arylisocyanate [e.g. phenylisocyanate, etc.] which may have halogen and its reactive derivative.

5 The suitable reactive derivative may be a conventional one such as an acid halide [e.g. acid chloride, acid bromide, etc.], an acid azide, an acid anhydride, an activated amide, an activated ester and the like.

10 When free acid is used as an acylating agent, the acylation reaction may preferably be conducted in the presence of a conventional condensing agent as mentioned above for Process 1.

15 The reaction can preferably be conducted in the presence of an organic or inorganic base such as alkali metal hydride [e.g. sodium hydride, potassium hydride, etc.], alkaline earth metal hydride [e.g. calcium hydride, magnesium hydride, etc.], alkali metal hydroxide [e.g. sodium hydroxide, potassium hydroxide, etc.], alkali metal carbonate [e.g. sodium carbonate, potassium carbonate, etc.], alkali metal 20 bicarbonate [e.g. sodium bicarbonate, potassium bicarbonate, etc.], alkali metal fluoride [e.g. potassium fluoride, cesium fluoride, etc.], alkali metal alkoxide [e.g. sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.], trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]-non-5-ene, 1,4-diazabicyclo-[2.2.2]octane, 25 1,5-diazabicyclo[5.4.0]undecene-5 or the like.

30 This reaction is usually carried out in a solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, tetrahydrofuran, chloroform, dioxane, pyridine, methylene chloride or the like.

35 The reaction temperature is not critical and the reaction can be carried out under coolint to heating.

Process 5

The compound [Ie] or its salt can be prepared by subjecting the compound [Ic] or its salt to alkylation reaction.

5 The alkylating agent to be used in the present alkylation reaction may include di(lower)alkyl sulfate [e.g. dimethyl sulfate, diethyl sulfate, etc.], diazo(lower)alkane [e.g. diazomethane, diazoethane, etc.], lower alkyl halide [e.g. methyl iodide, ethyl iodide, etc.], lower alkyl sulfonate [e.g. methyl p-toluenesulfonate, etc.], and the like.

10 The reaction using di(lower)alkyl sulfate, lower alkyl halide or lower alkyl sulfonate is usually carried out in a solvent such as water, acetone, ethanol, ether, dimethylformamide or any other solvent which does not adversely influence the reaction. The present reaction is preferably carried out in the presence of a base such as an inorganic base or an organic base as mentioned for Process 4. The reaction temperature is not critical and the reaction is usually carried out under cooling to heating around boiling point of the solvent.

15 The reaction using diazoalkane is usually carried out in a solvent such as ether, tetrahydrofuran or the like. The reaction temperature is not critical and the reaction is usually carried out under cooling or at ambient temperature.

20 The compound [Ie] or its salt can also be prepared by reacting the compound [Ic] or its salt with alkane aldehyde in the presence of reducing agent.

25 Suitable alkane aldehyde may include formaldehyde, acetaldehyde, propionaldehyde and the like.

30 Suitable reducing agent can be referred to the ones as mentioned above for Process 3. This reaction is usually carried out in a conventional solvent such as water, methanol, ethanol, propanol, tetralin,

tetrahydrofuran, acetonitrile, dioxane, chloroform, toluene, dimethylformamide, dimethylsulfoxide or any other organic solvent which does not adversely influence the reaction.

5 The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature or under cooling or warming.

Process 6

10 The object compound [If] or its salt can be prepared by reacting the compound [Ic] or its salt with the compound [IV].

Suitable example of the compound [IV] can be referred to the ones as mentioned above for Process 5.

15 The reaction is usually carried out in a solvent. A suitable solvent to be used may be water, alcohol [e.g. methanol, ethanol, propanol, etc.], acetonitrile, or any other conventional organic solvent such as diethyl ether, dioxane, tetrahydrofuran, etc. or a mixture thereof.

20 The reaction is preferably carried out under somewhat milder conditions such as under cooling to warming.

Process 7

25 The object compound [Ig] or its salt can be prepared by reducing the compound [If] or its salt.

30 This reaction may be carried out in substantially the same manner as Process 3, and therefore the reaction mode and reaction conditions [e.g. reducing agent, solvent, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 3.

(continued to the next page)

Process 8

The object compound [Ic] or its salt can be prepared by subjecting the compound [Ih] or its salt to hydrolysis. This reaction can be usually carried out in the presence 5 of an acid.

Suitable acid may be an organic acid (e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, benzenesulfonic acid, p-toluenesulfonic acid, etc.) and an inorganic acid (e.g. hydrochloric acid, hydrobromic 10 acid, sulfuric acid, phosphoric acid, etc.).

This reaction is preferably carried out in the presence of a trapping agent of aldehyde which is formed during the course of the reaction. Suitable trapping agent may be the compounds of the formula : $\text{NH}_2-\text{R}^{15}$ [VIII] 15 wherein R^{15} is hydroxy, lower alkoxy or amino, or salts thereof.

Suitable salts of the compound [VIII] may be an acid addition salt as described above.

This reaction is usually carried out in a conventional 20 solvent such as water, methanol, ethanol, propanol, tetralin, tetrahydrofuran, acetonitrile, dioxane, chloroform, toluene, dimethylformamide, dimethylsulfoxide or any other solvent which does not adversely influence the reaction, or a mixture thereof.

25 The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature or under cooling or warming or heating.

In the present reaction, in case that the compound 30 wherein Y is CO is used as a starting compound, said CO may be converted to C=N-OH during the reaction, which is also included within the scope of the reaction.

Process 9

The object compound [Ii] or its salt can be prepared 35 by reacting the compound [Ic] or its salt with the

compound [VI] or its salt.

This reaction is usually carried out in a conventional solvent such as water, methanol, ethanol, propanol, tetralin, tetrahydrofuran, dioxane, chloroform, dichloromethane, toluene, dimethylformamide, dimethylsulfoxide or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature or under warming to heating.

Process 10

The object compound [Ij] or its salt can be prepared by subjecting the compound [Ii] or its salt to reduction. The reduction may be carried out in substantially the same manner as Process 3, and therefore the reaction mode and reaction conditions [e.g. reducing agent, solvent, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 3.

Process 11

The object compound [Ik] or its salt can be prepared by reacting the compound [Ia] or its salt with the compound [VII] or its salt.

This reaction is usually carried out in a conventional solvent such as water, methanol, ethanol, propanol, tetralin, tetrahydrofuran, dioxane, chloroform, toluene, dimethylformamide, dimethylsulfoxide or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature or under warming to heating.

The compounds thus obtained by Processes 1 to 11 may be converted into aforesaid pharmaceutically acceptable salts thereof according to a conventional manner.

5 The new N-containing fused heterocyclic compounds [I] and pharmaceutical acceptable salts thereof possess antithrombotic activity, antiinflammatory activity, antiallergic activity and analgesic activity, and are useful for a therapeutic treatment of thrombosis [e.g. 10 cerebral thrombosis, etc.], inflammation [e.g. edema, etc.], and allergic disease [e.g. asthma, etc.], and are useful as analgesic.

15 For the purpose of showing pharmaceutical activity of the N-containing fused heterocyclic compounds [I], pharmacological test data of the representative compounds of the N-containing fused heterocyclic compounds [I] are illustrated in the following.

20 Platelet aggregation in vitro

1. Test method

25 Platelet rich plasma (PRP) which contains $6 - 7 \times 10^8$ platelets/ml was prepared from rabbit blood. To the 200 μ l of PRP, 5 μ l of calcium chloride (1 mM) and 50 μ l of 25mM Tris-acetate solution (pH 7.4) containing 120mM NaCl or test compound were added successively, and then stirred for 2 min. at 37°C. To the solution, 5 μ l of adenosine diphosphate (ADP) (2.5 μ M) or collagen (2.5 μ g/ml) was added as an aggregation inducer. Aggregation was measured by using an aggregometer (NKK HEMA-TRACER 1). Activities of inhibitors (test compounds) were expressed as ID_{50} values i.e. Doses required to inhibit the platelet aggregation responses by 50%.

35

2. Test result

Test compound	ADP	ID ₅₀ (M)	Collagen
Example 5	1.4 x 10 ⁻⁵	1.4 x 10 ⁻⁵	
Aspirin	3.2 x 10 ⁻³	3.1 x 10 ⁻⁵	

10

Platelet aggregation ex vivo

1. Test method

Male Sprague-Dawley rats weighing about 250 g were used after overnight fasting. One hour after oral administration of test compound or vehicle of test compound (control), blood was collected into a tube containing 0.1 vol. of 3.8% sodium citrate. To the 0.45 ml of blood, 0.05 ml of collagen (final concentration 5.0 µg/ml) was added and then incubated for 5 min. at 37°C. under shaking.

The reaction was terminated by addition of 1 ml of 10 mM phosphate buffered saline (pH 7.4) containing 11.5 mM EDTA and 1% formalin. The reaction mixture was centrifuged at 70xg for 5 min. and platelet count of upper phase was measured by Technicon Auto Analyzer.

Platelet aggregation was calculated according to the following formula:

$$\text{Platelet aggregation (\%)} = \frac{A - B}{A} \times 100$$

A; Platelet count after addition of vehicle of collagen

B; Platelet count after addition of collagen

Inhibition of the test compound was calculated according to the following formula;

$$\text{Inhibition (\%)} = \frac{C - D}{C} \times 100$$

5

- C. Platelet aggregation(%) of control
- D. Platelet aggregation(%) of Test compound

2. Test result

10

Test compound	Dose (mg/kg)	Inhibition (%)
Example 5	10	2
	32	67
	100	100

20

Carrageenin foot edema

1. Test method

Male Sprague-Dawley rats weighing about 180 g were used in groups of five.

25

Paw edema was induced by subplantar injection of 1% carrageenin (0.1 ml/rat) into the right hind paw in carrageenin foot edema. The test compound was suspended in methylcellulose and administered orally 60 minutes before phlogogen.

30

Paw volume was measured with plethysmometer (Ugo Basil Co., Ltd.) by water displacement immersing the paw to the lateral malleolus. The difference of paw volume before and 3 hours after the phlogogen was designated as edema volume.

35

The data was analyzed statistically by student's t-test.

2. Test result

5

Test compound	Dose (mg/kg)	Inhibition (%)
Example 5	320	40.0 *

10

note) * : $P < 0.05$

15

P : probability

Systemic anaphylaxis

1. Test method

20

Male Hartley guinea pigs (300-400g, n=5) were passively sensitized with i.v. injection of rabbit anti-ovalbumin serum. 24 Hours later, test compound was administered orally. 30 Min. after administration of test compound, sensitized animals were placed for 2 min. in a chamber filled with antigen aerosol (ovalbumin) by a conventional nebulizer. Survived animals were regarded as being protected from systemic anaphylaxis.

25

30

2. Test result

35

Test compound	Dose (mg/kg)	Survival (%)
Example 5	10	20
	100	100

Acetic acid-induced Writhing syndrome

1. Test method

5 Male Slc:ddy strain mice aged 6 weeks were used in groups of 10. The test compound was suspended in methylcellulose and administered orally. After 60 min., 20 ml/kg of 0.6% acetic acid solution was administered i.p. and writhing episodes between 3 and 13 min. after acetic acid injection were counted.

10 The data was analyzed statistically by student's t-test.

15 2. Test result

Test compound	Dose (mg/kg)	Inhibition (%)
Example 5	32	32.8 *

20 note) * : P < 0.01
 P : probability

25 For therapeutic administration, the object compounds [I] of the present invention and pharmaceutically acceptable salts thereof are used in a form of the conventional pharmaceutical preparation in admixture with a conventional pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral or external administration. The pharmaceutical preparation may be compounded in a solid form such as granule, capsule, tablet, dragee or suppository, or in a liquid form such as solution, suspension or emulsion.

If needed, there may be included in the above preparation auxiliary substance such as stabilizing agent, wetting or emulsifying agent, buffer or any other commonly used additives.

5 The effective ingredient may usually be administered with a unit dose of 0.01 mg/kg to 500 mg/kg, 1 to 4 times a day. However, the above dosage may be increased or decreased according to age, weight and conditions of the patient or the administering method.

10

The following preparations and examples are given only for the purpose of illustrating the present invention in more detail.

15

Preparation 1

3-Amino-5-chloro-2-mercaptopypyridine (18.8 g) was added to an ice-cooled solution of phosgene (30 g) in toluene (350 ml). 10% Aqueous solution of sodium hydroxide (300 ml) was added dropwise to the stirred mixture for a period of 1 hour below 20°C. The final mixture was stirred for 1.5 hours at ambient temperature and then stirred for an additional 1 hour at 50°C. After cooling, the aqueous layer was adjusted to pH 4.0 with 4N hydrochloric acid. The precipitates were collected by filtration, washed with water and dried over phosphorus pentoxide to give white powder of 6-chloro-2-oxo-1,2-dihydrothiazolo[5,4-b]pyridine (15.08 g).

20

IR (Nujol) : 3150, 3100, 3000, 1660, 1590, 1210, 1120, 900 cm^{-1}

25

NMR (DMSO- d_6 , δ) : 7.50 (1H, d, $J=2\text{Hz}$), 8.27 (1H, d, $J=2\text{Hz}$)

Preparation 2

Methyl chloroacetate (9.6 g) and potassium carbonate

30

(11.1 g) were added to a solution of 6-chloro-2-oxo-1,2-dihydrothiazolo[5,4-b]pyridine (15.0 g) in dry N,N-dimethylformamide (50 ml). The mixture was stirred for 30 minutes at 80°C and then poured into cold water. 5 The precipitates were collected by filtration, washed with water and dried over phosphorus pentoxide to give white powder of 6-chloro-1-methoxycarbonylmethyl-2-oxo-1,2-dihydrothiazolo[5,4-b]pyridine (20.52 g).

10 IR (Nujol) : 1740, 1690, 1590, 1310, 1230, 1180, 960, 900, 880, 710 cm^{-1}

NMR (CDCl_3 , δ) : 3.70 (3H, s), 4.65 (2H, s), 7.15 (1H, d, $J=2\text{Hz}$), 8.23 (1H, d, $J=2\text{Hz}$)

Preparation 3

15 An aqueous solution (30 ml) of potassium hydroxide (3.1 g) was added dropwise to an ice-cooled solution of 6-chloro-1-methoxycarbonylmethyl-2-oxo-1,2-dihydrothiazolo[5,4-b]pyridine (7.2 g) in tetrahydrofuran (70 ml). The mixture was stirred for 1 hour at ambient 20 temperature and then adjusted to pH 3.0 with 2N hydrochloric acid. After evaporation of tetrahydrofuran, the residue was extracted with ethyl acetate (50 ml x 5). The extracts were combined, dried over magnesium sulfate and 25 concentrated under reduced pressure to give a crystalline product, which was recrystallized from ethyl acetate (200 ml) to afford 6-chloro-1-carboxymethyl-2-oxo-1,2-dihydrothiazolo[5,4-b]pyridine (4.93 g) as crystals.

mp : 243-246°C

30 IR (Nujol) : 3450, 1725, 1690, 1590, 1430, 1310, 1220, 880, 720, 690 cm^{-1}

NMR (DMSO-d_6 , δ) : 4.83 (2H, s), 8.19 (1H, d, $J=2\text{Hz}$), 8.39 (1H, d, $J=2\text{Hz}$)

Example 1

35 To an ice-cooled solution of a mixture of

6-chloro-1-carboxymethyl-2-oxo-1,2-dihydrothiazolo-[5,4-b]pyridine (3.47 g) and N-hydroxysuccinimide (1.96 g) in N,N-dimethylformamide (20 ml) was gradually added N,N-dicyclohexylcarbodiimide (3.51 g). The mixture was stirred for 1 hour at ambient temperature and dicyclohexylurea that precipitated from the reaction mixture was removed by filtration. To a solution of piperazine (6.11 g) in N,N-dimethylformamide (80 ml) was added dropwise the filtrate for a period of 1.5 hours below 20°C. The final mixture was stirred for 4 hours at ambient temperature, and then filtered. The filtrate was concentrated under reduced pressure below 50°C and the residue was dissolved in 2N hydrochloric acid. The aqueous solution was washed with chloroform and then adjusted to pH 9 with an aqueous solution of sodium hydrogen carbonate. The turbid solution was extracted with chloroform, and the extract was dried over magnesium sulfate and concentrated under reduced pressure to give a white powder of 6-chloro-2-oxo-1-[(1-piperazinyl)-carbonylmethyl]-1,2-dihydrothiazolo[5,4-b]pyridine (3.24 g).

mp : 169-173°C

IR (Nujol) : 3300, 1710, 1640, 1580, 1420, 1310, 1250, 1190, 1120, 1040, 910, 880, 830, 790 cm^{-1}

NMR (CDCl_3 , δ) : 1.6-2.1 (1H, broad s), 2.8-3.2 (4H, m), 3.5-3.8 (4H, m), 4.75 (2H, s), 7.32 (1H, d, $J=2\text{Hz}$), 8.28 (1H, d, $J=2\text{Hz}$)

Example 2

To an ice-cooled solution of 2-oxo-3-benzothiazoline-acetic acid [J. Prakt. Chem. 27 (3-4), 220-4 (1965); 8.1g] and N-hydroxysuccinimide (5.4 g) in N,N-dimethylformamide (50 ml) was gradually added N,N-dicyclohexylcarbodiimide (9.6 g), and the mixture was stirred for an hour at ambient temperature. The dicyclohexylurea that

precipitated from the reaction mixture was filtered off. To a stirred solution of piperazine (16.7 g) in N,N-dimethylformamide (200 ml) was added dropwise the filtrate for a period of 40 minutes below 20°C. The 5 final mixture was stirred for 3.5 hours at ambient temperature and then filtered. The filtrate was concentrated under reduced pressure. The residue was dissolved in 2N hydrochloric acid and the solution was washed with chloroform. The aqueous layer was adjusted 10 to pH 9 with an aqueous solution of sodium hydrogen carbonate, and the turbid solution was extracted with chloroform (80 ml x 3). The extracts were combined and dried over magnesium sulfate. After evaporation of the solvent, 3-[(1-piperazinyl)carbonylmethyl]-2- 15 benzothiazolinone (9.50 g) was obtained as white powders.

mp : 197-201°C

IR (Nujol) : 3350, 1675, 1655, 1590, 1240, 755 cm^{-1}

NMR (DMSO-d₆, δ) : 1.0-2.0 (1H, broad s), 2.5-3.1 (4H, m), 3.1-3.6 (4H, m), 4.85 (2H, s), 20 7.0-7.7 (4H, m)

Example 3

To a solution of 6-chloro-2-oxo-1-[(1-piperazinyl)- 25 carbonylmethyl]-1,2-dihydrothiazolo[5,4-b]pyridine (1.40 g) in chloroform (15 ml) was added isoamyl nitrite (3.0 ml) and the mixture was stirred for 11 hours at room temperature. Precipitated crystals were collected by filtration, washed with chloroform and dried to give 30 colorless crystals of 6-chloro-2-oxo-1-[(4-nitroso-1-piperazinyl)carbonylmethyl]-1,2-dihydrothiazolo[5,4-b]-pyridine (1.33 g).

mp : 220-223°C (dec.)

IR (Nujol) : 1705, 1645, 1580, 1420, 990 cm^{-1}

NMR (DMSO-d₆, δ) : 3.5-4.0 (6H, m), 4.35 (2H, m), 35 5.04 (2H, s), 7.93 (1H, d, J=2Hz), 8.30 (1H, d, J=2Hz)

MASS : 341(M⁺), 311, 227 (Base), 199, 171

Example 4

To a solution of 3-[(1-piperazinyl)carbonylmethyl]-2-benzothiazolinone (3.0 g) in chloroform (50 ml) was added dropwise isoamyl nitrite (7.3 ml), for a period of 10 minutes below 20°C. The mixture was stirred for 18 hours at ambient temperature. Then, the reaction mixture was extracted with chloroform. The extract was washed with water, dried over magnesium sulfate and evaporated to give a crystalline product, which was recrystallized from a mixture of ethyl acetate and ethanol to give 3-[(4-nitroso-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone (2.54 g) as needles.

mp : 201-203°C

IR (Nujol) : 1680, 1640, 1590, 1480, 1430, 1340, 1290, 1260, 1230, 1195, 1155, 985, 795, 750 cm⁻¹

NMR (DMSO-d₆, δ) : 3.4-4.0 (6H, m), 4.1-4.6 (2H, m), 5.00 (2H, s), 7.0-7.8 (4H, m)

Example 5

5-Chloro-3-[(4-nitroso-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone (9.2 g) was dissolved in a mixture of water (120 ml) and acetic acid (400 ml). To the solution stirred at room temperature zinc dust (12.0 g) was added over 3 hours. The mixture was stirred for additional 2 hours at room temperature. The zinc dust unused in the reaction was filtered and washed once with acetic acid. The filtrate and the washing were combined and evaporated to dryness. Chloroform (200 ml) was added to the residue and insoluble material was then filtered. The chloroform solution was concentrated to give a syrup which was subjected to a silica gel column chromatography using a mixture of chloroform and methanol (10:1).

The desired fractions were combined and evaporated to give a pale yellow oil which was converted into hydrochloride using hydrogen chloride in absolute ether. The crude crystals obtained were recrystallized from aqueous ethanol to give 5-chloro-3-[(4-amino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone hydrochloride (4.03 g).

mp : 261-263°C

IR (Nujol) : 2740, 2650, 2570, 2070, 1670, 1640, 1590, 1535, 1465, 1350, 1250, 1100, 805 cm^{-1}

NMR (D_2O , δ) : 3.0-3.3 (4H, m), 3.6-4.0 (4H, m), 4.93 (2H, s), 7.0-7.6 (3H, m)

Elemental analysis

Calcd. for $\text{C}_{13}\text{H}_{15}\text{ClN}_4\text{O}_2\text{S} \cdot \text{HCl}$:

C, 42.98; H, 4.44; N, 15.42

Found : C, 43.14; H, 4.68; N, 15.54.

Example 6

To a solution of 6-chloro-2-oxo-1-[(4-nitroso-1-piperazinyl)carbonylmethyl]-1,2-dihydrothiazolo[5,4-b]-pyridine (1.42 g) in a mixture of acetic acid (30 ml) and water (9 ml) was added zinc dust (1.9 g) over 30 minutes with stirring at room temperature. The mixture was stirred for additional 2.5 hours at room temperature, then insoluble material was filtered and washed with acetic acid. The filtrate and the washings were combined and concentrated. The residue was subjected to column chromatography on silica gel (60 g) and eluted with a mixture of chloroform and methanol (10:1). The fractions containing the object compound were combined and concentrated. The crystalline residue (0.91 g) thus obtained was dissolved in ethanol (20 ml) and then a mixture of ethanol and hydrochloric acid solution was added thereto. The mixture was concentrated and the crystals (1.0 g) obtained were recrystallized from

methanol (50 ml) to give colorless crystals of 6-chloro-2-oxo-1-[(4-amino-1-piperazinyl)carbonylmethyl]-1,2-dihydrothiazolo[5,4-b]pyridine hydrochloride (0.71 g).

mp : 238-246°C (dec.)

5 IR (Nujol) : 2700, 2600, 1690, 1640, 1580, 1535, 1410, 1260, 1200 cm^{-1}

NMR (DMSO-d₆, δ) : 3.04 (4H, m), 3.63 (4H, broad s), 5.07 (2H, s), 8.02 (1H, d, J=2Hz), 8.38 (1H, d, J=2Hz), 9.90 (3H, broad s)

10 MASS : 327 (M⁺), 227, 199, 171, 71 (Base)

Elemental analysis

Calcd. for C₁₂H₁₄ClN₅O₂S·HCl

C, 39.57; H, 4.15; N, 19.23

Found : C, 39.82; H, 4.02; N, 19.38

15

Example 7

3-[(4-Nitroso-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone (2.37 g) was dissolved in a mixture of acetic acid (30 ml) and water (9 ml). Zinc powder

20 (3.54 g) was gradually added to the solution and the mixture was stirred for 1 hour at ambient temperature. After cooling, insoluble materials were filtered off and washed with acetic acid. The filtrate and washings

were combined and concentrated under reduced pressure.

25 The residue was dissolved in ethanol (200 ml) and an ethanolic solution of hydrogen chloride was added to the solution. The precipitates were filtered and recrystallized from a mixture of methanol (60 ml) and

30 water (20 ml) to give white powders of 3-[(4-amino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone hydrochloride (1.58 g).

mp : 249-258°C (dec.)

IR (Nujol) : 2750, 2700, 2620, 2080, 1670, 1640, 1610, 1545, 1260, 760 cm^{-1}

35 NMR (DMSO-d₆, δ) : 2.8-3.3 (4H, m), 3.3-3.9 (4H, m),

4.95 (2H, s), 7.0-7.5 (3H, m), 7.63 (1H, dd,
J=2 and 7.5Hz), 9.0-10.5 (3H, broad s)

Elemental analysis

Calcd. for $C_{13}H_{16}N_4O_2S \cdot HCl$:

5 C, 47.49; H, 5.21; N, 17.04
Found : C, 47.54; H, 5.02; N, 17.14

Example 8

10 A suspension of 5-chloro-3-[(4-amino-1-piperazinyl)-
carbonylmethyl]-2-benzothiazolinone hydrochloride (0.70 g)
in anhydrous pyridine (15 ml) was stirred for 1 hour at
room temperature and anhydrous acetic acid (0.5 ml) was
added thereto and stirred for additional 3 hours at
15 room temperature. To the reaction mixture was added
ice water and the resultant mixture was stirred for
10 minutes, then extracted with chloroform. The chloroform
layer was washed with water, dried and then concentrated.
Crystalline residue (0.58 g) obtained was recrystallized
20 from chloroform - methanol (2:1 V/V, 30 ml) to give
colorless crystals of 5-chloro-3-[(4-acetamido-1-
piperazinyl)carbonylmethyl]-2-benzothiazolinone (0.25 g).

mp : 284-285°C

IR (Nujol) : 3220, 1680, 1650 cm^{-1}

25 NMR (DMSO- d_6 , δ) : 1.73, 1.98 (3H, 2s), 2.6-3.0

(4H, m), 3.3-3.7 (4H, m), 4.96 (2H, s), 7.26 (1H, dd,
J=2 and 8Hz), 7.45 (1H, d, J=2Hz), 7.70 (1H, d,
J=8Hz), 8.50, 9.00 (1H, 2s)

MASS : 368 (M^+), 170, 43 (Base)

Elemental analysis

30 Calcd. for $C_{15}H_{17}ClN_4O_3S$:

C, 48.85; H, 4.65; N, 15.19

Found : C, 49.00; H, 4.57; N, 15.19

Example 9

35 Anhydrous acetic acid (2.08 ml) and formic acid

(0.83 ml) were mixed and reacted for 30 minutes at room temperature. To the above reaction mixture was added 5-chloro-3-[(4-amino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone (1.5 g) and stirred for 2 hours at room temperature. White crystals were filtered, washed with ethyl acetate and recrystallized from a mixture of chloroform and methanol to give colorless crystals of 5-chloro-3-[(4-formamido-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone (1.14 g).

10 mp : 256-258°C

IR (Nujol) : 3500, 3250, 1710, 1680, 1650, 1595, 1460 cm^{-1}

15 NMR (DMSO- d_6 , δ) : 2.6-2.9 (4H, m), 3.3-3.7 (4H, m), 4.95 (2H, s), 7.1-7.8 (3H, m), 8.18 (1H, d, $J=10\text{Hz}$), 9.07 (1H, d, $J=10\text{Hz}$)

MASS : 354 (M^+), 315, 198, 170, 84 (Base)

Elemental analysis

Calcd. for $\text{C}_{14}\text{H}_{15}\text{N}_4\text{ClO}_3\text{S} \cdot 2/3\text{MeOH}$:

C, 46.83; H, 4.73; N, 14.89

20 Found : C, 46.50; H, 4.49; N, 15.19

Example 10

To a solution of 5-chloro-3-[(4-amino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone (1.64 g) in methylene chloride (60 ml) were added potassium carbonate (860 mg) and mesyl chloride (0.96 ml) and stirred for 8 hours with reflux. Insoluble material was filtered off and the filtrate was evaporated and then recrystallized from a mixture of chloroform and methanol to give colorless crystals of 5-chloro-3-[(4-mesylamino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone (1.2 g).

mp : 202-203°C

IR (Nujol) : 3230, 1680, 1655, 1595, 1460 cm^{-1}

35 NMR (DMSO- d_6 , δ) : 2.7-3.0 (4H, m), 2.97 (3H, s), 3.3-3.8 (4H, m), 4.96 (2H, s), 7.22 (1H, dd,

J=8, 2Hz), 7.43 (1H, d, J=2Hz), 7.68 (1H, d, J=8Hz), 8.42 (1H, s)

MASS : 403 (M⁺-1), 389, 324, 198, 170, 99 (Base)

Elemental analysis

5 Calcd. for C₁₄H₁₇ClN₄O₄S₂ :

C, 41.53; H, 4.23; N, 13.84

Found : C, 41.07; H, 4.05; N, 13.84

Example 11

10 A mixture of 5-chloro-3-[(4-amino-1-piperazinyl)-carbonylmethyl]-2-benzothiazolinone (0.85 g), anhydrous potassium carbonate (430 mg), dichloromethane (40 ml), dioxane (10 ml) and ethyl chloroformate (339 mg) was stirred for 1.5 hours at room temperature. The insoluble materials were filtered off and the filtrate was concentrated under reduced pressure. The residue was recrystallized from a mixture of chloroform and dioxane to give colorless crystals of 5-chloro-3-[(4-ethoxy-carbonylamino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone (0.35 g).

20 mp : 160-163°C (dec.)

IR (Nujol) : 3240, 1710, 1665, 1590, 1550, 1460 cm⁻¹

25 NMR (DMSO-d₆, δ) : 1.16 (3H, t, J=7Hz), 2.6-3.0 (4H, m), 3.4-3.7 (4H, m), 4.02 (2H, q, J=7Hz), 4.97 (2H, s), 7.1-7.8 (3H, m), 8.38 (1H, s)

MASS : 398 (M⁺), 352, 310, 226, 198 (Base), 170

Elemental analysis

30 Calcd. for C₁₆H₁₉N₄ClO₄S·1/4C₄H₈O₂ :

C, 48.51; H, 5.03; N, 13.31

Found : C, 48.55; H, 5.02; N, 13.22

Example 12

35 A solution of 4-fluorobenzoyl chloride (761 mg) in dioxane (3 ml) was added dropwise to a mixture of

5-chloro-3-[(4-amino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone hydrochloride (872 mg), 1N-NaOH (5.3 ml), dioxane (30 ml) and water (5 ml) at 5°C. The resulting mixture was stirred for 30 minutes and concentrated under reduced pressure. The residue obtained was filtered, washed with water and ethyl acetate, and recrystallized from methanol to give 5-chloro-3-[(4-(4-fluorobenzamido)-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone (0.61 g).

10 IR (Nujol) : 3220, 1710, 1665, 1640, 1600, 1510, 1460 cm^{-1}

NMR ($\text{CF}_3\text{CO}_2\text{H}$, δ) : 4.0-4.6 (8H, m), 5.18 (2H, s), 7.1-7.6 (5H, m), 7.9-8.2 (2H, m)

Elemental analysis

15 Calcd. for $\text{C}_{20}\text{H}_{18}\text{ClFN}_4\text{O}_3\text{S}$:
C, 53.51; H, 4.04; N, 12.48
Found : C, 53.87; H, 4.18; N, 12.52

Example 13

20 A solution of 4-fluorophenyl isocyanate (273 mg) in dioxane (5 ml) was added dropwise to a mixture of 5-chloro-3-[(4-amino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone hydrochloride (981 mg), triethylamine (273 mg), dioxane (40 ml) and water (2 ml) at room temperature. The resulting mixture was stirred for 25 2 hours and concentrated under reduced pressure. The residue was filtered, washed with water and ethyl acetate, and recrystallized from N,N-dimethylformamide to give 5-chloro-3-[(4-[N'-(4-fluorophenyl)ureido]-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone (0.82 g).

30 mp : >250°C

IR (Nujol) : 3650, 3430, 3300, 1680, 1660, 1590, 1530, 1510, 1460 cm^{-1}

NMR ($\text{CF}_3\text{CO}_2\text{H}$, δ) : 3.8-4.6 (8H, m), 5.20 (2H, s), 6.9-7.6 (7H, m), 8.3 (1H, broad s)

35 MASS : 463 (M^+), 326, 226, 198, 170, 111 (Base)

Elemental analysis

Calcd. for $C_{20}H_{19}N_5ClFO_3S$:

C, 51.82; H, 4.13; N, 15.10

Found : C, 51.12; H, 4.42; N, 14.78

5

Example 14

To a solution of 5-chloro-3-[(4-amino-1-piperazinyl)-carbonylmethyl]-2-benzothiazolinone (1.64 g) in acetonitrile (50 ml) were added 37% formaldehyde solution (4 ml) and sodium cyanoborohydride (1 g) and the mixture was stirred for 25 minutes at room temperature and further for 1 hour neutralizing with acetic acid and concentrated. To a residue was added saturated sodium carbonate solution and extracted with chloroform.

10 After drying over anhydrous magnesium sulfate, the solution was concentrated under reduced pressure. The residue was subjected to a column chromatography on silica gel (42 g) and eluted with a mixture of chloroform-methanol (20:1). The fractions containing the object compound were combined and concentrated under reduced pressure. The residue was washed with ether and then acetic acid to give 5-chloro-3-[(4-dimethylamino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone (0.32 g), which was dissolved with heating in a mixture of chloroform (10 ml) and ethanol (5 ml). After cooling, to the mixture was added ethanol solution containing hydrogen chloride (about 23%). The residue obtained by concentration under reduced pressure was recrystallized from a mixture of ethanol (10 ml) and water (0.5 ml) to give colorless crystals of 5-chloro-3-[(4-dimethylamino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone hydrochloride (0.31 g).

15

20

25

30

mp : 192-194°C

IR (Nujol) : 3550, 2380, 1680, 1630, 1490 cm^{-1}

35 NMR (DMSO- d_6 , δ) : 2.85 (6H, s), 2.8-3.2 (4H, m),

3.4-3.8 (4H, m), 4.96 (2H, s), 7.20 (1H, dd,
J=8, 2Hz), 7.43 (1H, d, J=2Hz), 7.68 (1H, d,
J=8Hz)

MASS : 354 (M⁺, Base), 226, 198, 170, 128

5 Elemental analysis

Calcd. for C₁₅H₂₀Cl₂N₄O₂S·H₂O :
C, 44.02; H, 5.41; N, 13.69

Found : C, 44.13; H, 5.17; N, 13.59

10 Example 15

A solution of 5-chloro-3-[(4-amino-1-piperazinyl)-carbonylmethyl]-2-benzothiazolinone (5.0 g) and 37% formaldehyde solution (1.38 ml) in acetonitrile (150 ml) was stirred for 1.5 hours at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel (50 g) eluting with a mixture of chloroform and methanol (50:1). The fractions containing the desired compound were combined and concentrated under reduced pressure. The residue was recrystallized from ethanol (200 ml) to give colorless crystals of 5-chloro-3-[(4-methyleneamino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone (5.1 g).

mp : 150-152°C

25 IR (Nujol) : 1685, 1650, 1590, 1465 cm⁻¹

NMR (DMSO-d₆, δ) : 2.8-3.2 (4H, m), 3.5-3.8 (4H, m), 4.96 (2H, s), 6.28, 6.58 (2H, ABq, J=10Hz), 7.1-7.8 (3H, m)

MASS : 338 (M⁺), 310, 226, 198, 170, 18 (Base)

30 Elemental analysis

Calcd. for C₁₄H₁₅N₄ClO₂S :
C, 49.63; H, 4.46; N, 16.54
Found : C, 49.77; H, 4.32; N, 16.57

Example 16

A mixture of 5-chloro-3-[(4-methyleneamino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone (5.09 g), sodium borohydride (284 mg), tetrahydrofuran (80 ml), and ethanol (70 ml) was stirred for 3 hours at room temperature. The reaction mixture was concentrated under reduced pressure and the residue obtained was purified by column chromatography on silica gel eluting with a mixture of chloroform and methanol (20:1). The fractions containing the desired compound were combined and concentrated under reduced pressure. The white residue was dissolved in chloroform (5 ml), and 20% solution of hydrogen chloride in ethanol (1 ml) was added to the above solution. The white precipitates were filtered and recrystallized from a mixture of ethanol (10 ml) and water (2 ml) to give colorless crystals of 5-chloro-3-[(4-methylamino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone hydrochloride (0.5 g).

mp : 248-250°C

IR (Nujol) : 3400, 2650, 2500, 1710, 1670, 1595 cm^{-1}

NMR (DMSO-d₆, δ) : 2.69 (3H, s), 2.8-3.8 (8H, m), 4.96 (2H, s), 7.1-7.8 (3H, m), 10.8 (2H, broad s)

MASS : 340 (M⁺), 310, 226, 198 (Base), 170

Elemental analysis

Calcd. for C₁₄H₁₈Cl₂N₄O₂S :

C, 44.57; H, 4.81; N, 14.85

Found : C, 44.32; H, 4.52; N, 14.84

30

(continued to the next page)

35

Example 17

In a similar manner to that of Example 1, 2 or 23, there were obtained the following compounds.

5 (1) 5-Chloro-3-[(1-piperazinyl)carbonylmethyl]-2-benzoxazolinone
mp : 161-171°C
IR (Nujol) : 3300, 1785, 1650 cm^{-1}
NMR (DMSO- d_6 , δ) : 1.0-2.0 (1H, br s), 2.5-3.0
10 (4H, m), 3.3-3.7 (4H, m), 7.15 (1H, dd, $J=7.5\text{Hz}$
and 2Hz), 7.40 (1H, d, $J=7.5\text{Hz}$), 7.45 (1H, d,
 $J=2\text{Hz}$)
MASS (m/e) : 295 (M^+), 182, 113, 85, 56 (base)

15 (2) 4-Chloro-3-[(1-piperazinyl)carbonylmethyl]-2-benzothiazolinone
mp : 165-166.5°C
IR (Nujol) : 3350, 1670, 1650 cm^{-1}
NMR (CDCl₃, δ) : 1.70 (1H, br s), 2.8-3.1 (4H, m),
20 3.4-3.7 (4H, m), 5.20 (2H, s), 6.8-7.4 (3H, m)

25 (3) 6-Chloro-3-[(1-piperazinyl)carbonylmethyl]-2-benzothiazolinone
mp : 166-168°C
IR (Nujol) : 3340, 1690, 1650 cm^{-1}
NMR (CDCl₃, δ) : 1.75 (1H, br s), 2.7-3.1 (4H, m),
3.4-3.7 (4H, m), 4.65 (2H, s), 6.92 (1H, d,
 $J=8\text{Hz}$), 7.22 (1H, dd, $J=8\text{Hz}$ and 2Hz), 7.38
(1H, d, $J=2\text{Hz}$)

30 (4) 7-Chloro-3-[(1-piperazinyl)carbonylmethyl]-2-benzothiazolinone
mp : 169-172°C
IR (Nujol) : 3320, 1680, 1650 cm^{-1}
NMR (CDCl₃, δ) : 1.65 (1H, br s), 2.75-3.00 (4H, m),

3.45-3.65 (4H, m), 4.96 (2H, s), 6.90 (1H, dd, J=2.5Hz and 7.0Hz), 7.08 (1H, dd, J=2.5Hz and 7.0Hz), 7.20 (1H, dd, J=7.0Hz)

5 (5) 5-Methyl-3-[(1-piperazinyl)carbonylmethyl]-2-benzothiazolinone
mp : 185-188°C
IR (Nujol) : 3370, 1690, 1640 cm^{-1}
NMR (CDCl_3 , δ) : 1.70 (1H, broad s), 2.7-3.1 (4H, m), 3.5-3.8 (4H, m), 4.67 (2H, s), 6.7-7.4 (3H, m)

10 (6) 5-Trifluoromethyl-3-[(1-piperazinyl)carbonylmethyl]-2-benzothiazolinone
mp : 162-163°C
IR (Nujol) : 3320, 1690, 1650, 1120 cm^{-1}
NMR (CDCl_3 , δ) : 1.73 (1H, br s), 2.8-3.1 (4H, m), 3.5-3.7 (4H, m), 4.80 (2H, s), 7.23 (1H, s), 7.42 (1H, d, J=8Hz), 7.56 (1H, d, J=8Hz)

15 (7) 5-Chloro-3-[(1-homopiperazinyl)carbonylmethyl]-2-benzothiazolinone
mp : 179-180°C
IR (Nujol) : 1680, 1640 cm^{-1}
NMR (CDCl_3 , δ) : 1.6-2.1 (3H, m), 2.7-3.2 (4H, m), 3.5-3.8 (4H, m), 4.70 (2H, s), 7.0-7.4 (3H, m)

20 (8) 5-Chloro-3-[(3-methyl-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone
mp : 153-155°C
IR (Nujol) : 1690, 1650 cm^{-1}
NMR (CDCl_3 , 60°C, δ) : 1.07 (3H, d, J=6Hz), 2.4-3.2 (5H, m), 3.7-4.3 (2H, m), 4.65 (2H, s), 7.00 (1H, s), 7.15 (1H, d, J=8Hz), 7.25 (1H, d, J=8Hz)

25

30

35

(9) 5-Chloro-6-phenyl-3-[(1-piperazinyl)carbonylmethyl]-2-benzothiazolinone

mp : 150-153°C

IR (Nujol) : 3300, 1685, 1645 cm^{-1}

5 NMR (CDCl_3 , δ) : 1.73 (1H, s), 2.8-3.2 (4H, m), 3.5-3.8 (4H, m), 4.73 (2H, s), 7.13 (1H, s), 7.43 (6H, br s)

(10) 5-Chloro-6-bromo-3-[(1-piperazinyl)carbonylmethyl]-2-benzothiazolinone

10 mp : 186-189°C

IR (Nujol) : 3340, 1690, 1645, 1580, 1470 cm^{-1}

15 NMR (DMSO-d_6 , δ) : 2.5-3.0 (4H, m), 3.3-3.7 (4H, m), 4.90 (2H, s), 7.63 (1H, s), 8.13 (1H, s)

(11) 6-Chloro-1-[(4-benzylideneamino-1-piperazinyl)-carbonylmethyl]-2,3-indolinedione

mp : 241-243°C

20 IR (Nujol) : 1755, 1735, 1665, 1620, 1375, 1255, 1130, 1100, 1000 cm^{-1}

(12) 6-Chloro-3-[(4-benzylideneamino-1-piperazinyl)-carbonylmethyl]-2-iminobenzothiazoline

25 mp : 158-160°C (dec.)

IR (Nujol) : 3350, 1625, 1575, 990, 800, 750 cm^{-1}

Example 18

30 In a similar manner to that of Example 3 or 4, there were obtained the following compounds.

(1) 5-Chloro-3-[(4-nitroso-1-piperazinyl)carbonylmethyl]-2-benzoxazolinone

mp : 212-215°C (dec.)

35 IR (Nujol) : 1775, 1660 cm^{-1}

NMR (DMSO-d_6 , δ) : 3.3-4.1 (6H, m), 4.2-4.7 (2H, m)

4.93 (2H, s), 7.13 (1H, dd, $J=7.5\text{Hz}$ and 2Hz),
7.38 (1H, d, $J=7.5\text{Hz}$), 7.45 (1H, d, $J=2\text{Hz}$)

(2) 4-Chloro-3-[(4-nitroso-1-piperazinyl)carbonylmethyl]-
5 2-benzothiazolinone

mp : 179-180°C

IR (Nujol) : 1695, 1675 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.5-4.1 (6H, m), 4.2-4.6 (2H, m),
10 5.28 (2H, s), 7.15 (1H, dd, $J=7.5\text{Hz}$), 7.38 (1H,
dd, $J=7.5\text{Hz}$, 2Hz), 7.68 (1H, dd, $J=7.5\text{Hz}$ and
2Hz)

(3) 6-Chloro-3-[(4-nitroso-1-piperazinyl)carbonylmethyl]-
15 2-benzothiazolinone

mp : 177-179°C

IR (Nujol) : 1685, 1650 cm^{-1}

NMR (DMSO- d_6 , δ) : 3.5-4.1 (6H, m), 4.2-4.6
(2H, m), 5.00 (2H, s), 7.2-7.5 (2H, m),
7.80 (1H, d, $J=2.0\text{Hz}$)

20

(4) 7-Chloro-3-[(4-nitroso-1-piperazinyl)carbonylmethyl]-
2-benzothiazolinone

mp : 227-230°C (dec.)

IR (Nujol) : 1690, 1650 cm^{-1}

25

NMR (DMSO- d_6 , δ) : 3.4-4.0 (6H, m), 4.1-4.5 (2H, m),
5.00 (2H, s), 7.1-7.5 (3H, m)

30

(5) 5-Methyl-3-[(4-nitroso-1-piperazinyl)carbonylmethyl]-
2-benzothiazolinone

mp : 214-217°C

IR (Nujol) : 1680, 1650 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.35 (3H, s), 3.5-4.1 (6H, m),
4.2-4.6 (2H, m), 4.97 (2H, s), 7.02 (1H, d,
 $J=8\text{Hz}$), 7.07 (1H, s), 7.50 (1H, d, $J=8\text{Hz}$)

35

(6) 5-Trifluoromethyl-3-[(4-nitroso-1-piperazinyl)-carbonylmethyl]-2-benzothiazolinone

mp : 216-218°C

IR (Nujol) : 1690, 1650 cm^{-1}

5 NMR (DMSO-d₆, δ) : 3.5-4.1 (6H, m), 4.3-4.7 (2H, m), 5.15 (2H, s), 7.60 (1H, d, J=8Hz), 7.73 (1H, s), 8.00 (1H, d, J=8Hz)

(7) 5-Chloro-3-[(4-nitroso-1-homopiperazinyl)-carbonylmethyl]-2-benzothiazolinone

10 mp : 171-172°C

IR (Nujol) : 1680, 1650 cm^{-1}

15 NMR (CDCl₃, δ) : 1.8-2.3 (2H, m), 3.4-4.1 (6H, m), 4.3-4.8 (4H, m), 6.9-7.5 (3H, m)

(8) 5-Chloro-3-[(3-methyl-4-nitroso-1-piperazinyl)-carbonylmethyl]-2-benzothiazolinone

mp : 193-194°C

20 IR (Nujol) : 1680, 1650 cm^{-1}

NMR (DMSO-d₆, 60°C, δ) : 1.07 and 1.47 (3H, 2d, J=7Hz), 3.1-4.4 (5H, m), 4.4-4.9 (2H, m), 4.95 (2H, s), 7.15 (1H, dd, J=8Hz and 2Hz), 7.31 (1H, d, J=2Hz), 7.59 (1H, d, J=8Hz)

25 (9) 5-Chloro-6-phenyl-3-[(4-nitroso-1-piperazinyl)-carbonylmethyl]-2-benzothiazolinone

mp : 263-266°C

IR (Nujol) : 1680, 1660 cm^{-1}

30 (10) 5-Chloro-6-bromo-3-[(4-nitroso-1-piperazinyl)-carbonylmethyl]-2-benzothiazolinone

mp : >260°C

IR (Nujol) : 1680, 1590 cm^{-1}

35 (11) 5-Chloro-3-[(4-nitroso-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone

mp : 212-214°C

IR (Nujol) : 1670, 1590 cm^{-1}

Example 19

5 In a similar manner to that of Example 5, 6 or 7
there were obtained the following compounds.

(1) 5-Chloro-3-[(4-amino-1-piperazinyl)carbonylmethyl]-
2-benzoxazolinone hydrochloride

10 mp : 240-242°C (dec.)

IR (Nujol) : 2650, 2600, 1775, 1650, 1600, 1540,
1250, 1030, 935, 810, 690 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.8-3.2 (4H, m), 3.5-3.8 (4H, m),
4.90 (2H, s), 7.15 (1H, dd, $J=9\text{Hz}$ and 2Hz),
15 7.38 (1H, d, $J=9\text{Hz}$), 7.45 (1H, d, $J=2\text{Hz}$),
9.4-10.4 (1H, broad s)

MASS (m/e) : 310 (M^+), 182, 71 (base)

Analysis Calcd. for $C_{13}H_{15}ClN_4O_3 \cdot HCl$

C 44.97, H 4.64, N 16.14

20 Found : C 44.74, H 4.97, N 16.08

(2) 4-Chloro-3-[(4-amino-1-piperazinyl)carbonylmethyl]-
2-benzothiazolinone hydrochloride

mp : 237-251°C (dec.)

25 IR (Nujol) : 2760, 2700, 2610, 1665, 1630 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.8-3.2 (4H, m), 3.5-3.9 (4H, m),
5.21 (2H, s), 7.18 (1H, d, $J=7.5\text{Hz}$), 7.38
(1H, dd, $J=7.5\text{Hz}$ and 2.0Hz), 7.70 (1H, dd,
 $J=7.5\text{Hz}$ and 2Hz), 9.5-10.3 (3H, broad s)

30 MASS (m/e) : 326 (M^+), 226, 198 (base), 170, 71

Analysis Calcd. for $C_{13}H_{15}ClN_4O_2S \cdot HCl$

C 42.98, H 4.44, N 15.42

Found : C 42.93, H 4.69, N 15.52

35 (3) 6-Chloro-3-[(4-amino-1-piperazinyl)carbonylmethyl]-
2-benzothiazolinone hydrochloride

mp : 215-243°C (dec.)

IR (Nujol) : 2700, 2600, 1670, 1650 cm^{-1}

NMR (DMSO-d₆, δ) : 2.9-3.3 (4H, m), 3.5-3.8 (4H, m), 4.99 (2H, s), 7.25 (1H, d, J=8Hz), 7.42 (1H, dd, J=8Hz and 2Hz), 7.82 (1H, d, J=2Hz), 9.2-10.5 (3H, br s)

MASS (m/e) : 326 (M⁺), 198, 170, 71, 36 (base)

Analysis Calcd. for C₁₃H₁₅ClN₄O₂S·HCl·1/2H₂O
C 41.94, H 4.60, N 15.05

10 Found : C 41.75, H 4.46, N 15.19

(4) 7-Chloro-3-[(4-amino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone hydrochloride

15 mp : 233-242°C (dec.)

IR (Nujol) : 2750-2600, 1690, 1670 cm^{-1}

NMR (DMSO-d₆, δ) : 2.8-3.2 (4H, m), 3.4-3.8 (4H, m), 5.00 (2H, s), 7.1-7.5 (3H, m), 9.2-9.9 (3H, broad s)

MASS (m/e) : 326 (M⁺, base)

20 Analysis Calcd. for C₁₃H₁₅ClN₄O₂S·HCl
C 42.98, H 4.44, N 15.42

Found : C 42.57, H 4.65, N 15.38

(5) 5-Methyl-3-[(4-amino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone hydrochloride

25 mp : 230-240°C (dec.)

IR (Nujol) : 2750, 2670, 2610, 1670, 1645 cm^{-1}

NMR (DMSO-d₆, δ) : 2.34 (3H, s), 2.8-3.2 (4H, m), 3.4-3.8 (4H, m), 4.92 (2H, s), 7.00 (1H, d, J=7.5Hz), 7.04 (1H, s), 7.49 (1H, d, J=7.5Hz), 9.3-10.3 (3H, broad s)

MASS (m/e) : 306 (M⁺), 206, 178, 150, 71 (base)

Analysis Calcd. for C₁₄H₁₈N₄O₂S·HCl
C 49.05, H 5.59, N 16.34

35 Found : C 49.13, H 5.61, N 16.46

(6) 5-Trifluoromethyl-3-[(4-amino-1-piperazinyl)-carbonylmethyl]-2-benzothiazolinone hydrochloride
mp : 250-260°C (dec.)

5 IR (Nujol) : 2750, 2670, 1690, 1655 cm^{-1}
NMR (DMSO-d₆, δ) : 2.8-3.2 (4H, m), 3.5-3.8 (4H, m),
5.07 (2H, s), 7.48 (1H, d, J=7.5Hz), 7.60
(1H, s), 7.87 (1H, d, J=7.5Hz), 9.3-9.9 (3H,
broad s)

10 MASS (m/e) : 360 (M⁺), 204, 71 (base)

Analysis Calcd. for C₁₄H₁₅F₃N₄O₂S·HCl·1/2H₂O
C 41.44, H 4.22, N 13.81
Found : C 41.51, H 4.45, N 13.81

(7) 5-Chloro-3-[(4-amino-1-homopiperazinyl)carbonyl-methyl]-2-benzothiazolinone hydrochloride
15 mp : 228-232°C

20 IR (Nujol) : 3280, 3160, 2570, 1710, 1660, 1620,
1590, 1180, 1080, 900, 800 cm^{-1}
NMR (DMSO-d₆, δ) : 1.8-2.3 (2H, m), 2.9-3.9
(8H, m), 4.95 (2H, s), 7.25 (1H, dd, J=8Hz
and 2Hz), 7.48 (1H, d, J=2Hz), 7.71 (1H, d,
J=8Hz), 8.8-10.5 (3H, broad s)

25 Analysis Calcd. for C₁₄H₁₇ClN₄O₂S·HCl
C 44.57, H 4.81, N 14.85
Found : C 44.91, H 4.87, N 14.92

(8) 5-Chloro-3-[(4-amino-3-methyl-1-piperazinyl)-carbonylmethyl]-2-benzothiazolinone hydrochloride
mp : 168-170°C

30 IR (Nujol) : 3400, 2670, 2600, 1680, 1655 cm^{-1}
NMR (DMSO-d₆, 60°C, δ) : 1.22 (3H, d, J=5Hz),
2.7-3.6 (5H, m), 3.8-4.2 (2H, m), 4.94 (2H, s),
7.15 (1H, dd, J=8Hz and 2Hz), 7.33 (1H, d,
J=2Hz), 7.58 (1H, d, J=8Hz), 8.0-10.0 (3H,
broad s)

Analysis Calcd. for $C_{14}H_{17}ClN_4O_2S \cdot HCl \cdot H_2O$
C 42.54, H 5.10, N 14.17
Found : C 42.97, H 5.12, N 13.80

5 (9) 5-Chloro-6-phenyl-3-[(4-amino-1-piperazinyl)-
carbonylmethyl]-2-benzothiazolinone hydrochloride
mp : > 270°C
IR (Nujol) : 2700, 2600, 1690, 1655, 1600, 1535,
1460, 1260, 1245, 1175, 1075, 990 cm^{-1}
10 NMR (DMSO-d₆, δ) : 2.9-3.3 (4H, m), 3.6-3.9
(4H, m), 5.07 (2H, s), 7.5-7.8 (7H, m),
9.8 (3H, br s)

15 (10) 5-Chloro-6-bromo-3-[(4-amino-1-piperazinyl)-
carbonylmethyl]-2-benzothiazolinone hydrochloride
mp : 263-265°C (dec.)
IR (Nujol) : 2650, 2600, 1705, 1660, 1590, 1520,
1470, 1380, 1350, 1310, 1240, 1190,
1070, 990 cm^{-1}
20 NMR (DMSO-d₆, δ) : 2.8-3.3 (4H, m), 3.5-3.9 (4H,
m), 5.00 (2H, s), 7.70 (1H, s), 8.17 (1H, s),
9.7 (3H, br s)

25 (11) 6-Chloro-1-[(4-amino-1-piperazinyl)carbonylmethyl]-
3-hydroxyimino-2-indolinone hydrochloride
mp : 209-214°C
IR (Nujol) : 2600, 1715, 1640, 1610, 1380, 1270,
1250, 1200, 1100, 1040, 1025 cm^{-1}
NMR (DMSO-d₆, δ) : 2.8-3.3 (4H, m), 3.4-3.8 (4H, m),
4.77 (2H, s), 7.13 (1H, d, J=8Hz), 7.20 (1H, s),
7.97 (1H, d, J=8Hz)
MASS (m/e) : 337 (M⁺), 320 (base peak)

35 (12) 6-Chloro-3-[(4-amino-1-piperazinyl)carbonylmethyl]-
2-iminobenzothiazoline

mp : 137-142°C (dec.)

IR (Nujol) : 3250, 1655, 1610, 1585, 1240, 1160,
1025, 960, 800 cm^{-1}

5 NMR (CDCl_3 , δ) : 2.58 (4H, t, $J=5\text{Hz}$), 3.64 (4H, t,
 $J=5\text{Hz}$), 4.70 (2H, s), 6.75 (1H, d, $J=8\text{Hz}$),
7.10 (1H, dd, $J=2\text{Hz}$ and 8Hz), 7.15 (1H, d,
 $J=2\text{Hz}$)

MASS (m/e) : 325 (M^+), 309 (base), 225

10 (13) 6-Nitro-3-[(4-amino-1-piperazinyl)carbonylmethyl]-
2-benzothiazolinone hydrochloride

mp : 240-242°C

15 IR (Nujol) : 2700, 2600, 1680, 1650, 1605, 1590,
1515, 1460, 1380, 1340, 1250, 1195,
895 cm^{-1}

NMR (DMSO-d_6 , δ) : 2.9-3.9 (8H, m), 5.13 (2H, s),
7.50 (1H, d, $J=9\text{Hz}$), 8.30 (1H, dd, $J=9\text{Hz}$, 3Hz),
8.77 (1H, d, $J=3\text{Hz}$), 9.8 (3H, br s)

20 Example 20

A mixture of 5-chloro-3-[(4-amino-1-piperazinyl)-
carbonylmethyl]-2-benzothiazolinone hydrochloride (2.6 g),
N-(p-nitrobenzyloxycarbonyl)acetamidine (2.0 g) and
dichloromethane (24 ml) in ethanol (50 ml) was refluxed
25 for 3 hours. The mixture was concentrated under reduced
pressure. The residue was subjected to column
chromatography on silica gel (100 g) eluting with a mixture
of chloroform and methanol (20:1). The fractions
containing the desired compound were combined and
30 evaporated to give pale yellow powders of 5-chloro-3-
{[4-[(N-(p-nitrobenzyloxycarbonyl)acetimidoylamino]-1-
piperazinyl]carbonylmethyl]-2-benzothiazolinone (3.2 g).

IR (Film) : 3300, 1750, 1695, 1680, 1660, 1630,
1590, 1520 cm^{-1}

35 NMR (DMSO-d_6 , δ) : 2.1-2.9 (7H, m), 3.4-3.8 (4H, m),

4.95 (2H, s), 5.30 (2H, s), 7.1-7.8 (5H, m),
8.1-8.4 (3H, m)

Example 21

5 A mixture of 5-chloro-3-[4-[N-(p-nitrobenzyloxy-carbonyl)acetimidoylamino]-1-piperazinyl]carbonylmethyl]-2-benzothiazolinone (2.0 g), acetic acid (0.3 ml), water (3 ml), 10% palladium on carbon (2.0 g) in tetrahydrofuran (40 ml) and methanol (20 ml) was
10 incubated under an atmosphere of hydrogen for 3 hours. Palladium on carbon was filtered off, and the filtrate was coevaporated with ethanol. The residue obtained was purified by aluminum column chromatography, treated with hydrogen chloride in ethanol, and recrystallized
15 from a mixture of water, ethanol and ether to give yellow crystals of 5-chloro-3-[(4-acetimidoylamino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone hydrochloride (0.3 g).

mp : 194-200°C

20 IR (Nujol) : 3400, 1695, 1660, 1595, 1470 cm^{-1}
NMR (DMSO- d_6 , δ) : 2.16 (3H, s), 2.6-3.1 (4H, m),
3.5-4.0 (4H, m), 5.01 (2H, s), 7.2-7.8 (3H, m),
8.77 (1H, s), 9.56 (1H, s), 11.52 (1H, s)
MASS (m/e) : 368 (M^+ , base), 334, 198

25 Analysis Calcd. for $\text{C}_{15}\text{H}_{19}\text{N}_5\text{Cl}_2\text{O}_2\text{S} \cdot 2/3\text{H}_2\text{O}$
C 43.28, H 4.92, N 16.82

Found : C 43.18, H 5.26, N 16.58

Example 22

30 To a solution of 5-chloro-3-[(1-piperazinyl)carbonylmethyl]-2-benzothiazolinone (3.0 g) in a mixture of N,N-dimethylformamide (30 ml) and water (5 ml) was added S-methylisothiourea sulfate (4.0 g). The mixture was stirred for 8 hours at 80°C and then cooled. The
35 precipitates formed were filtered and recrystallized

from water (100 ml) to give 5-chloro-3-[(4-amidino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone hemisulfate (2.63 g).

mp : 282-285°C (dec.)

5 IR (Nujol) : 3350, 3070, 1705, 1660, 1610 cm^{-1}
NMR (DMSO-d₆, δ) : 3.3-4.0 (8H, m), 4.97 (2H, s),
7.19 (1H, dd, J=7.5Hz and 2Hz), 7.43 (1H, d,
J=2Hz), 7.62 (1H, d, J=7.5Hz), 7.9-9.0 (4H,
broad s)

10 Analysis Calcd. for C₁₄H₁₆ClN₅O₂S·1/2H₂SO₄
C 41.74, H 4.25, N 17.38
Found : C 41.29, H 4.44, N 17.34

Example 23

15 (1) Piperazine (86.14 g, 1 mol) was dissolved in a cooled mixture of acetic acid (300 g) and water (430 ml). To this solution was added dropwise a solution of sodium nitrite (69 g, 1 mol) dissolved in water (172 ml) at 10°C, and the reaction mixture was stirred for an hour at the same temperature. Then zinc powder (172.3 g) was added to the solution containing 1-nitrosopiperazine by portions below 40°C, and after addition, the reaction mixture was stirred for additional an hour and filtered. The cake of zinc was washed with water (172 ml), and benzaldehyde (106.1 g) dissolved in 424 ml of ethanol was added to the combined solution containing 1-aminopiperazine of the filtrate and washings. After stirring for an hour at room temperature, ethyl acetate (1034 ml) and ammonium chloride (281.4 g) was added to the mixture and the pH was adjusted to 9.50 with 6N sodium hydroxide solution. The insoluble materials in the organic layer was filtered off, and the aqueous layer was extracted again with ethyl acetate (690 ml). The combined extract containing 1-benzylideneaminopiperazine was dried over magnesium sulfate, and after filtration,

magnesium sulfate was washed with 300 ml of methylene chloride and the washings were combined with the filtrate.

5 (2) To a suspension of 3-carboxymethyl-5-chloro-
2-benzothiazolinone (121.84 g, 0.5 mol) in a mixed
solvent of methylene chloride (610 ml) and dimethyl-
formamide (61 ml), was added thionyl chloride (61 g),
and the mixture was stirred under reflux for an hour.
10 To the solution of 1-benzylideneaminopiperazine
obtained by the reaction (1) was added triethylamine
(126.5 g), and the above-mentioned solution of the acid
chloride dropwise below 0°C. After addition, the
reaction mixture was stirred for an hour at the same
15 temperature. The mixture was concentrated to one third
volume and methanol (1200 ml) was added. The precipitates
were filtered, washed with methanol (1200 ml) and dried
to give 5-chloro-3-[(4-benzylideneamino-1-piperazinyl)-
carbonylmethyl]-2-benzothiazolinone (189.0 g).

20 mp : 213-215°C
 IR (Nujol) : 1700 (sh), 1680, 1650, 1590 cm^{-1}
 NMR (DMSO- d_6 , δ) : 2.87-3.47 (4H, m), 3.47-3.93
 (4H, m), 5.00 (2H, s), 7.10-7.87 (9H, m)

25 Example 24

In a similar manner to that of Example 1, 2 or 23, there were obtained the following compounds.

(1) 5-Chloro-3-[(4-(2-hydroxybenzylideneamino)-1-piperazinyl]carbonylmethyl]-2-benzothiazolinone
30 mp : 206-207°C
IR (Nujol) : 1690, 1660, 1590 cm^{-1}
NMR (DMSO- d_6 , δ) : 3.0-3.5 (4H, m), 3.5-4.1 (4H, m),
5.00 (2H, s), 7.3-7.8 (8H, m), 11.07 (1H, s)

(2) 5-Chloro-3-[(4-isobutylideneamino-1-piperazinyl)-carbonylmethyl]-2-benzothiazolinone
mp : 147-149°C
IR (Nujol) : 1690, 1650, 1590 cm^{-1}
5 NMR (CDCl_3 , δ) : 1.05 (6H, d, $J=7\text{Hz}$), 2.45 (1H, sept, $J=7\text{Hz}$), 3.00 (4H, m), 3.73 (4H, m), 4.70 (2H, s), 6.87-7.43 (4H, m)

(3) 6-Nitro-3-[(4-benzylideneamino-1-piperazinyl)-carbonylmethyl]-2-benzothiazolinone
10 mp : 248-250°C
IR (Nujol) : 1690, 1660, 1460, 1340, 1250, 1140, 990 cm^{-1}

15 (4) 6-Chloro-2-oxo-1-[(4-nitroso-1-piperazinyl)-carbonylmethyl]-1,2-dihydrothiazolo[5,4-b]pyridine
mp : 220-223°C (dec.)
IR (Nujol) : 1705, 1645, 1580, 1420, 990 cm^{-1}
20 NMR (DMSO-d_6 , δ) : 3.5-4.0 (6H, m), 4.35 (2H, m), 5.04 (2H, s), 7.93 (1H, d, $J=2\text{Hz}$), 8.30 (1H, d, $J=2\text{Hz}$)
MASS : 341 (M^+), 311, 227 (Base), 199, 171

(5) 3-[(4-Nitroso-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone
25 mp : 201-203°C
IR (Nujol) : 1680, 1640, 1590, 1480, 1430, 1340, 1290, 1260, 1230, 1195, 1155, 985, 795, 750 cm^{-1}
30 NMR (DMSO-d_6 , δ) : 3.4-4.0 (6H, m), 4.1-4.6 (2H, m), 5.00 (2H, s), 7.0-7.8 (4H, m)

(6) 5-Chloro-3-[(4-amino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone hydrochloride
35 mp : 261-263°C

IR (Nujol) : 2740, 2650, 2570, 2070, 1670, 1640,
1590, 1535, 1465, 1350, 1250, 1100, 805 cm^{-1}

NMR (D_2O , δ) : 3.0-3.3 (4H, m), 3.6-4.0 (4H, m),
4.93 (2H, s), 7.0-7.6 (3H, m)

5 Elemental analysis

Calcd. for $\text{C}_{13}\text{H}_{15}\text{ClN}_4\text{O}_2\text{S}\cdot\text{HCl}$:
C 42.98, H 4.44, N 15.42

Found : C 43.14, H 4.68, N 15.54

10 (7) 6-Chloro-2-oxo-1-[(4-amino-1-piperazinyl)carbonyl-methyl]-1,2-dihydrothiazolo[5,4-b]pyridine hydrochloride

mp : 238-246°C (dec.)

15 IR (Nujol) : 2700, 2600, 1690, 1640, 1580, 1535,
1410, 1260, 1200 cm^{-1}

NMR (DMSO-d_6 , δ) : 3.04 (4H, m), 3.63 (4H, broad s),
5.07 (2H, s), 8.02 (1H, d, $J=2\text{Hz}$), 8.38 (1H, d,
 $J=2\text{Hz}$), 9.90 (3H, broad s)

MASS : 327 (M^+), 227, 199, 171, 71 (Base)

20 Elemental analysis

Calcd. for $\text{C}_{12}\text{H}_{14}\text{ClN}_5\text{O}_2\text{S}\cdot\text{HCl}$
C 39.57, H 4.15, N 19.23

Found : C 39.82, H 4.02, N 19.38

25 (8) 3-[(4-Amino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone hydrochloride

mp : 249-258°C (dec.)

IR (Nujol) : 2750, 2700, 2620, 2080, 1670, 1640,
1610, 1545, 1260, 760 cm^{-1}

30 NMR (DMSO-d_6 , δ) : 2.8-3.3 (4H, m), 3.3-3.9 (4H,
m), 4.95 (2H, s), 7.0-7.5 (3H, m), 7.63 (1H,
 $dd, J=2\text{Hz}$ and 7.5Hz), 9.0-10.5 (3H, broad s)

Elemental analysis

Calcd. for $\text{C}_{13}\text{H}_{16}\text{N}_4\text{O}_2\text{S}\cdot\text{HCl}$:
C 47.49, H 5.21, N 17.04
Found : C 47.54, H 5.02, N 17.14

(9) 5-Chloro-3-[(4-acetamido-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone

mp : 284-285°C

IR (Nujol) : 3220, 1680, 1650 cm^{-1}

5 NMR (DMSO-d₆, δ) : 1.73, 1.98 (3H, 2s), 2.6-3.0 (4H, m), 3.3-3.7 (4H, m), 4.96 (2H, s), 7.26 (1H, dd, J=2Hz and 8Hz), 7.45 (1H, d, J=2Hz), 7.70 (1H, d, J=8Hz), 8.50, 9.00 (1H, 2s)

MASS : 368 (M⁺), 170, 43 (Base)

10 Elemental analysis

Calcd. for C₁₅H₁₇ClN₄O₃S :

C 48.85, H 4.65, N 15.19

Found : C 49.00, H 4.57, N 15.19

15 (10) 5-Chloro-3-[(4-formamido-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone

mp : 256-258°C

IR (Nujol) : 3500, 3250, 1710, 1680, 1650, 1595, 1460 cm^{-1}

20 NMR (DMSO-d₆, δ) : 2.6-2.9 (4H, m), 3.3-3.7 (4H, m), 4.95 (2H, s), 7.1-7.8 (3H, m), 8.18 (1H, d, J=10Hz), 9.07 (1H, d, J=10Hz)

MASS : 354 (M⁺), 315, 198, 170, 84 (Base)

Elemental analysis

25 Calcd. for C₁₄H₁₅N₄ClO₃S·2/3MeOH :

C 46.83, H 4.73, N 14.89

Found : C 46.50, H 4.49, N 15.19

30 (11) 5-Chloro-3-[(4-mesylamino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone

mp : 202-203°C

IR (Nujol) : 3230, 1680, 1655, 1595, 1460 cm^{-1}

35 NMR (DMSO-d₆, δ) : 2.7-3.0 (4H, m), 2.97 (3H, s), 3.3-3.8 (4H, m), 4.96 (2H, s), 7.22 (1H, dd, J=8Hz, 2Hz), 7.43 (1H, d, J=2Hz), 7.68 (1H, d, J=8Hz), 8.42 (1H, s)

MASS : 403 ($M^+ - 1$), 389, 324, 198, 170, 99 (Base)
Elemental analysis

Calcd. for $C_{14}H_{17}ClN_4O_4S_2$:
C 41.53, H 4.23, N 13.84
5 Found : C 41.07, H 4.05, N 13.84

(12) 5-Chloro-3-[(4-ethoxycarbonylamino-1-piperazinyl)-carbonylmethyl]-2-benzothiazolinone

mp. : 160-163°C (dec.)

10 IR (Nujol) : 3240, 1710, 1665, 1590, 1550,
1460 cm^{-1}

NMR (DMSO- d_6 , δ) : 1.16 (3H, t, $J=7\text{Hz}$), 2.6-3.0
(4H, m), 3.4-3.7 (4H, m), 4.02 (2H, q, $J=7\text{Hz}$),
4.97 (2H, s), 7.1-7.8 (3H, m), 8.38 (1H, s)

15 MASS : 398 (M^+), 352, 310, 226, 198 (Base), 170

Elemental analysis

Calcd. for $C_{16}H_{19}N_4ClO_4S \cdot 1/4C_4H_8O_2$:
C 48.51, H 5.03, N 13.31
Found : C 48.55, H 5.02, N 13.22

20

(13) 5-Chloro-3-[(4-(4-fluorobenzamido)-1-piperazinyl)-carbonylmethyl]-2-benzothiazolinone

IR (Nujol) : 3220, 1710, 1665, 1640, 1600, 1510,
1460 cm^{-1}

25 NMR (CF_3CO_2H , δ) : 4.0-4.6 (8H, m), 5.18 (2H, s),
7.1-7.6 (5H, m), 7.9-8.2 (2H, m)

Elemental analysis

Calcd. for $C_{20}H_{18}ClFN_4O_3S$:
C 53.51, H 4.04, N 12.48

30 Found : C 53.87, H 4.18, N 12.52

(14) 5-Chloro-3-[(4-[N'-(4-fluorophenyl)ureido]-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone

mp. : >250°C

35 IR (Nujol) : 3650, 3430, 3300, 1680, 1660, 1590,
1530, 1510, 1460 cm^{-1}

NMR ($\text{CF}_3\text{CO}_2\text{H}$, δ) : 3.8-4.6 (8H, m), 5.20 (2H, s),
6.9-7.6 (7H, m), 8.3 (1H, broad s)

MASS : 463 (M^+), 326, 226, 198, 170, 111 (Base)

Elemental analysis

5

Calcd. for $\text{C}_{20}\text{H}_{19}\text{N}_5\text{ClFO}_3\text{S}$:

C 51.82, H 4.13, N 15.10

Found : C 51.12, H 4.42, N 14.78

10 (15) 5-Chloro-3-[(4-dimethylamino-1-piperazinyl)-
carbonylmethyl]-2-benzothiazolinone hydrochloride
mp : 192-194°C

IR (Nujol) : 3550, 2380, 1680, 1630, 1490 cm^{-1}

15 NMR (DMSO- d_6 , δ) : 2.85 (6H, s), 2.8-3.2 (4H, m),
3.4-3.8 (4H, m), 4.96 (2H, s), 7.20 (1H, dd,
J=8Hz, 2Hz), 7.43 (1H, d, J=2Hz), 7.68 (1H, d,
J=8Hz)

MASS : 354 (M^+ , Base), 226, 198, 170, 128

Elemental analysis

20

Calcd. for $\text{C}_{15}\text{H}_{20}\text{Cl}_2\text{N}_4\text{O}_2\text{S} \cdot \text{H}_2\text{O}$:

C 44.02, H 5.41, N 13.69

Found : C 44.13, H 5.17, N 13.59

25

(16) 5-Chloro-3-[(4-methyleneamino-1-piperazinyl)-
carbonylmethyl]-2-benzothiazolinone

mp : 150-152°C

IR (Nujol) : 1685, 1650, 1590, 1465 cm^{-1}

30 NMR (DMSO- d_6 , δ) : 2.8-3.2 (4H, m), 3.5-3.8
(4H, m), 4.96 (2H, s), 6.28, 6.58 (2H, ABq,
J=10Hz), 7.1-7.8 (3H, m)

MASS : 338 (M^+), 310, 226, 198, 170, 18 (Base)

Elemental analysis

35

Calcd. for $\text{C}_{14}\text{H}_{15}\text{N}_4\text{ClO}_2\text{S}$:

C 49.63, H 4.46, N 16.54

Found : C 49.77, H 4.32, N 16.57

(17) 5-Chloro-3-[(4-methylamino-1-piperazinyl)-carbonylmethyl]-2-benzothiazolinone hydrochloride
mp : 248-250°C
IR (Nujol) : 3400, 2650, 2500, 1710, 1670, 1595 cm^{-1}
5 NMR (DMSO-d₆, δ) : 2.69 (3H, s), 2.8-3.8 (8H, m),
4.96 (2H, s), 7.1-7.8 (3H, m), 10.8 (2H,
broad s)
MASS : 340 (M⁺), 310, 226, 198 (Base), 170
Elemental analysis
10 Calcd. for C₁₄H₁₈Cl₂N₄O₂S :
C 44.57, H 4.81, N 14.85
Found : C 44.32, H 4.52, N 14.84

(18) 5-Chloro-3-[(4-nitroso-1-piperazinyl)carbonylmethyl]-2-benzoxazolinone
15 mp : 212-215°C (dec.)
IR (Nujol) : 1775, 1660 cm^{-1}
NMR (DMSO-d₆, δ) : 3.3-4.1 (6H, m), 4.2-4.7 (2H, m),
20 4.93 (2H, s), 7.13 (1H, dd, J=7.5Hz and 2Hz),
7.38 (1H, d, J=7.5Hz), 7.45 (1H, d, J=2Hz)

(19) 4-Chloro-3-[(4-nitroso-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone
25 mp : 179-180°C
IR (Nujol) : 1695, 1675 cm^{-1}
NMR (DMSO-d₆, δ) : 3.5-4.1 (6H, m), 4.2-4.6 (2H, m),
5.28 (2H, s), 7.15 (1H, dd, J=7.5Hz),
7.38 (1H, dd, J=7.5Hz, 2Hz), 7.68 (1H, dd,
J=7.5Hz and 2Hz)

(20) 6-Chloro-3-[(4-nitroso-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone
30 mp : 177-179°C
IR (Nujol) : 1685, 1650 cm^{-1}
NMR (DMSO-d₆, δ) : 3.5-4.1 (6H, m), 4.2-4.6 (2H, m),

5.00 (2H, s), 7.2-7.5 (2H, m), 7.80 (1H, d,
J=20Hz)

5 (21) 7-Chloro-3-[(4-nitroso-1-piperazinyl)carbonyl-methyl]-2-benzothiazolinone

mp : 227-230°C (dec.)

IR (Nujol) : 1690, 1650 cm^{-1}

NMR (DMSO-d₆, δ) : 3.4-4.0 (6H, m), 4.1-4.5 (2H, m),
5.00 (2H, s), 7.1-7.5 (3H, m)

10

(22) 5-Methyl-3-[(4-nitroso-1-piperazinyl)carbonyl-methyl]-2-benzothiazolinone

mp : 214-217°C

IR (Nujol) : 1680, 1650 cm^{-1}

15

NMR (DMSO-d₆, δ) : 2.35 (3H, s), 3.5-4.1 (6H, m),
4.2-4.6 (2H, m), 4.97 (2H, s), 7.02 (1H, d,
J=8Hz), 7.07 (1H, s), 7.50 (1H, d, J=8Hz)

20

(23) 5-Trifluoromethyl-3-[(4-nitroso-1-piperazinyl)-carbonylmethyl]-2-benzothiazolinone

mp : 216-218°C

IR (Nujol) : 1690, 1650 cm^{-1}

25

NMR (DMSO-d₆, δ) : 3.5-4.1 (6H, m), 4.3-4.7 (2H, m),
5.15 (2H, s), 7.60 (1H, d, J=8Hz), 7.73 (1H, s),
8.00 (1H, d, J=8Hz)

30

(24) 5-Chloro-3-[(4-nitroso-1-homopiperazinyl)carbonyl-methyl]-2-benzothiazolinone

mp : 171-172°C

IR (Nujol) : 1680, 1650 cm^{-1}

NMR (CDCl₃, δ) : 1.8-2.3 (2H, m), 3.4-4.1 (6H, m),
4.3-4.8 (4H, m), 6.9-7.5 (3H, m)

35

(25) 5-Chloro-3-[(3-methyl-4-nitroso-1-piperazinyl)-carbonylmethyl]-2-benzothiazolinone

mp : 193-194°C

IR (Nujol) : 1680, 1650 cm^{-1}

NMR (DMSO- d_6 , 60°C, δ) : 1.07 and 1.47 (3H, 2d, J=7Hz), 3.1-4.4 (5H, m), 4.4-4.9 (2H, m), 4.95 (2H, s), 7.15 (1H, dd, J=8Hz and 2Hz), 7.31 (1H, d, J=2Hz), 7.59 (1H, d, J=8Hz)

5

(26) 5-Chloro-6-phenyl-3-[(4-nitroso-1-piperazinyl)-carbonylmethyl]-2-benzothiazolinone

10

mp : 263-266°C

IR (Nujol) : 1680, 1660 cm^{-1}

(27) 5-Chloro-6-bromo-3-[(4-nitroso-1-piperazinyl)-carbonylmethyl]-2-benzothiazolinone

15

mp : >260°C

IR (Nujol) : 1680, 1590 cm^{-1}

(28) 5-Chloro-3-[(4-nitroso-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone

20

mp : 212-214°C

IR (Nujol) : 1670, 1590 cm^{-1}

(29) 5-Chloro-3-[(4-amino-1-piperazinyl)carbonylmethyl]-2-benzoxazolinone hydrochloride

25

mp : 240-242°C (dec.)

IR (Nujol) : 2650, 2600, 1775, 1650, 1600, 1540, 1250, 1030, 935, 810, 690 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.8-3.2 (4H, m), 3.5-3.8 (4H, m), 4.90 (2H, s), 7.15 (1H, dd, J=9Hz and 2Hz), 7.38 (1H, d, J=9Hz), 7.45 (1H, d, J=2Hz), 9.4-10.4 (1H, broad s)

MASS (m/e) : 310 (M^+), 182, 71 (base)

Analysis Calcd. for $C_{13}H_{15}ClN_4O_3 \cdot HCl$
C 44.97, H 4.64, N 16.14

35

Found : C 44.74, H 4.97, N 16.08

(30) 4-Chloro-3-[(4-amino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone hydrochloride

mp : 237-251°C (dec.)

IR (Nujol) : 2760, 2700, 2610, 1665, 1630 cm^{-1}

5 NMR (DMSO-d₆, δ) : 2.8-3.2 (4H, m), 3.5-3.9 (4H, m), 5.21 (2H, s), 7.18 (1H, dd, J=7.5Hz), 7.38 (1H, dd, J=7.5Hz and 2.0Hz), 7.70 (1H, dd, J=7.5Hz and 2Hz), 9.5-10.3 (3H, broad s)

10 MASS (m/e) : 326 (M⁺), 226, 198 (Base), 170, 71

Analysis Calcd. for C₁₃H₁₅ClN₄O₂S·HCl

C 42.98, H 4.44, N 15.42

Found : C 42.93, H 4.69, N 15.52

(31) 6-Chloro-3-[(4-amino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone hydrochloride

mp : 215-243°C (dec.)

IR (Nujol) : 2700, 2600, 1670, 1650 cm^{-1}

15 NMR (DMSO-d₆, δ) : 2.9-3.3 (4H, m), 3.5-3.8 (4H, m), 4.99 (2H, s), 7.25 (1H, d, J=8Hz), 7.42 (1H, dd, J=8Hz and 2Hz), 7.82 (1H, d, J=2Hz), 9.2-10.5 (3H, br s)

20 MASS (m/e) : 326 (M⁺), 198, 170, 71, 36 (Base)

Analysis Calcd. for C₁₃H₁₅ClN₄O₂S·HCl·1/2H₂O

C 41.94, H 4.60, N 15.05

25 Found : C 41.75, H 4.46, N 15.19

(32) 7-Chloro-3-[(4-amino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone hydrochloride

mp : 233-242°C (dec.)

30 IR (Nujol) : 2750-2600, 1690, 1670 cm^{-1}

NMR (DMSO-d₆, δ) : 2.8-3.2 (4H, m), 3.4-3.8 (4H, m), 5.00 (2H, s), 7.1-7.5 (3H, m), 9.2-9.9 (3H, broad s)

MASS (m/e) : 326 (M⁺, base)

35 Analysis Calcd for C₁₃H₁₅ClN₄O₂S·HCl

C 42.98, H 4.44, N 15.42

Found : C 42.57, H 4.65, N 15.38

(33) 5-Methyl-3-[(4-amino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone hydrochloride

mp : 230-240°C (dec.)

IR (Nujol) : 2750, 2670, 2610, 1670, 1645 cm^{-1}

5 NMR (DMSO-d₆, δ) : 2.34 (3H, s), 2.8-3.2 (4H, m), 3.4-3.8 (4H, m), 4.92 (2H, s), 7.00 (1H, d, J=7.5Hz), 7.04 (1H, s), 7.49 (1H, d, J=7.5Hz), 9.3-10.3 (3H, broad s)

MASS (m/e) : 306 (M⁺), 206, 178, 150, 71 (Base)

10 Analysis Calcd. for C₁₄H₁₈N₄O₂S·HCl

C 49.05, H 5.59, N 16.34

Found : C 49.13, H 5.61, N 16.46

(34) 5-Trifluoromethyl-3-[(4-amino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone hydrochloride

15 mp : 250-260°C (dec.)

IR (Nujol) : 2750, 2670, 1690, 1655 cm^{-1}

NMR (DMSO-d₆, δ) : 2.8-3.2 (4H, m), 3.5-3.8 (4H, m), 5.07 (2H, s), 7.48 (1H, d, J=7.5Hz), 7.60 (1H, s), 7.87 (1H, d, J=7.5Hz), 9.3-9.9 (3H, broad s)

20 MASS (m/e) : 360 (M⁺), 204, 71 (Base)

Analysis Calcd. for C₁₄H₁₅F₃N₄O₂S·HCl·1/2H₂O

C 41.44, H 4.22, N 13.81

25 Found : C 41.51, H 4.45, N 13.81

(35) 5-Chloro-3-[(4-amino-1-homopiperazinyl)carbonylmethyl]-2-benzothiazolinone hydrochloride

mp : 228-232°C

30 IR (Nujol) : 3280, 3160, 2570, 1710, 1660, 1620, 1590, 1180, 1080, 900, 800 cm^{-1}

NMR (DMSO-d₆, δ) : 1.8-2.3 (2H, m), 2.9-3.9 (8H, m), 4.95 (2H, s), 7.25 (1H, dd, J=8Hz and 2Hz), 7.48 (1H, d, J=2Hz), 7.71 (1H, d, J=8Hz), 8.8-10.5 (3H, broad s)

Analysis Calcd. for $C_{14}H_{17}ClN_4O_2S \cdot HCl$
C 44.57, H 4.81, N 14.85
Found : C 44.91, H 4.87, N 14.92

5 (36) 5-Chloro-3-[(4-amino-3-methyl-1-piperazinyl)-
carbonylmethyl]-2-benzothiazolinone hydrochloride
mp : 168-170°C
IR (Nujol) : 3400, 2670, 2600, 1680, 1655 cm^{-1}
NMR (DMSO-d₆, 60°C, δ) : 1.22 (3H, d, J=5Hz),
10 2.7-3.6 (5H, m), 3.8-4.2 (2H, m), 4.94 (2H, s),
7.15 (1H, dd, J=8Hz and 2Hz), 7.33 (1H, d,
J=2Hz), 7.58 (1H, d, J=8Hz), 8.0-10.0 (3H,
broad s)

15 Analysis Calcd. for $C_{14}H_{17}ClN_4O_2S \cdot HCl \cdot H_2O$
C 42.54, H 5.10, N 14.17
Found : C 42.97, H 5.12, N 13.80

20 (37) 5-Chloro-6-phenyl-3-[(4-amino-1-piperazinyl)-
carbonylmethyl]-2-benzothiazolinone hydrochloride
mp : >270°C
IR (Nujol) : 2700, 2600, 1690, 1655, 1600, 1535,
1460, 1260, 1245, 1175, 1075, 990 cm^{-1}
NMR (DMSO-d₆, δ) : 2.9-3.3 (4H, m), 3.6-3.9 (4H,
25 m), 5.07 (2H, s), 7.5-7.8 (7H, m), 9.8 (3H,
br s)

30 (38) 5-Chloro-6-bromo-3-[(4-amino-1-piperazinyl)-
carbonylmethyl]-2-benzothiazolinone hydrochloride
mp : 263-265°C (dec.)
IR (Nujol) : 2650, 2600, 1705, 1660, 1590, 1520,
1470, 1380, 1350, 1310, 1240, 1190, 1070,
990 cm^{-1}
NMR (DMSO-d₆, δ) : 2.8-3.3 (4H, m), 3.5-3.9 (4H, m),
35 5.00 (2H, s), 7.70 (1H, s), 8.17 (1H, s),
9.7 (3H, br s)

(39) 5-Chloro-3-[(4-[N-(p-nitrobenzylloxycarbonyl)-acetimidoylamino]-1-piperazinyl]carbonylmethyl]-2-benzothiazolinone

5 IR (Film) : 3300, 1750, 1695, 1680, 1660, 1630, 1590, 1520 cm^{-1}

NMR (DMSO-d₆, δ) : 2.1-2.9 (7H, m), 3.4-3.8 (4H, m), 4.95 (2H, s), 5.30 (2H, s), 7.1-7.8 (5H, m), 8.1-8.4 (3H, m)

10 (40) 5-Chloro-3-[(4-acetimidoylamino-1-piperazinyl)-carbonylmethyl]-2-benzothiazolinone hydrochloride

mp : 194-200 °C

15 IR (Nujol) : 3400, 1695, 1660, 1595, 1470 cm^{-1}

NMR (DMSO-d₆, δ) : 2.16 (3H, s), 2.6-3.1 (4H, m), 3.5-4.0 (4H, m), 5.01 (2H, s), 7.2-7.8 (3H, m), 8.77 (1H, s), 9.56 (1H, s), 11.52 (1H, s)

MASS (m/e) : 368 (M⁺, base), 334, 198

Analysis Calcd. for C₁₅H₁₉N₅Cl₂O₂S·2/3H₂O :
C 43.28, H 4.92, N 16.82

20 Found : C 43.18, H 5.26, N 16.58

(41) 5-Chloro-3-[(4-amidino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone hemisulfate

25 mp : 282-285 °C (dec.)

IR (Nujol) : 3350, 3070, 1705, 1660, 1610 cm^{-1}

NMR (DMSO-d₆, δ) : 3.3-4.0 (8H, m), 4.97 (2H, s), 7.19 (1H, dd, J=7.5Hz and 2Hz), 7.43 (1H, d, J=2Hz), 7.62 (1H, d, J=7.5Hz), 7.9-9.0 (4H, broad s)

30 Analysis Calcd. for C₁₄H₁₆ClN₅O₂S·1/2H₂SO₄
C 41.74, H 4.25, N 17.38

Found : C 41.29, H 4.44, N 17.34

(42) 6-Chloro-3-[(4-amino-1-piperazinyl)carbonylmethyl]-2-iminobenzothiazoline

mp : 137-142°C (dec.)

IR (Nujol) : 3250, 1655, 1610, 1585, 1240, 1160,
1025, 960, 800 cm^{-1}

5 NMR (CDCl_3 , δ) : 2.58 (4H, t, $J=5\text{Hz}$), 3.64 (4H, t,
J=5Hz), 4.70 (2H, s), 6.75 (1H, d, $J=8\text{Hz}$),
7.10 (1H, dd, $J=2\text{Hz}$ and 8Hz), 7.15 (1H, d,
J=2Hz)

MASS (m/e) : 325 (M^+), 309 (base), 225

10 (43) 6-Nitro-3-[(4-amino-1-piperazinyl)carbonylmethyl]-
2-benzothiazolinone hydrochloride

mp : 240-242°C

15 IR (Nujol) : 2700, 2600, 1680, 1650, 1605,
1590, 1515, 1460, 1380, 1340, 1250,
1195, 895 cm^{-1}

NMR (DMSO-d_6 , δ) : 2.9-3.9 (8H, m), 5.13 (2H, s),
7.50 (1H, d, $J=9\text{Hz}$), 8.30 (1H, dd, $J=9\text{Hz}$, 3Hz),
8.77 (1H, d, $J=3\text{Hz}$), 9.8 (3H, br s)

20 (44) 6-Chloro-1-[(4-amino-1-piperazinyl)carbonylmethyl]-
3-hydroxyimino-2-indolinone hydrochloride

mp : 209-214°C

IR (Nujol) : 2600, 1715, 1640, 1610, 1380, 1270,
1250, 1200, 1100, 1040, 1025 cm^{-1}

25 NMR (DMSO-d_6 , δ) : 2.8-3.3 (4H, m), 3.4-3.80
(4H, m), 4.77 (2H, s), 7.13 (1H, d, $J=8\text{Hz}$),
7.20 (1H, s), 7.97 (1H, d, $J=8\text{Hz}$)

MASS (m/e) : 337 (M^+), 320 (base peak)

30 Example 25

To a solution of hydroxylamine hydrochloride (25.2 g) in a mixed solvent of acetonitrile (300 ml) and 6N-hydrochloric acid (150 ml), was added 5-chloro-3-[(4-benzylideneamino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone (15 g). The resulting solution was

5

stirred overnight at room temperature. After stirring for five hours under ice cooling, the crystalline precipitates were filtered, and washed successively with water (30 ml) and methylene chloride (75 ml). This product was suspended in water (30 ml) and then filtered to give 5-chloro-3-[(4-amino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone hydrochloride (8.60 g).

mp : 261-263°C

10

IR (Nujol) : 2740, 2650, 2570, 2070, 1670, 1640, 1590, 1535, 1465, 1350, 1250, 1100, 805 cm^{-1}

NMR (D_2O , δ) : 3.0-3.3 (4H, m), 3.6-4.0 (4H, m), 4.93 (2H, s), 7.0-7.6 (3H, m)

Elemental analysis

15

Calcd. for $\text{C}_{13}\text{H}_{15}\text{ClN}_4\text{O}_2\text{S} \cdot \text{HCl}$:

C 42.98, H 4.44, N 15.42

Found : C 43.14, H 4.68, N 15.54

Example 26

20

To a solution of hydroxylamine hydrochloride (3.2 g) in a mixed solvent of acetonitrile (40 ml) and 6N-hydrochloric acid (20 ml) was added 5-chloro-3-[(4-(2-hydroxybenzylideneamino)-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone (2 g). The resulting solution was stirred overnight at room temperature. After stirring for five hours under ice cooling, the crystalline precipitates were filtered, and washed successively with water (4 ml) and methylene chloride (10 ml). This product was further washed by suspending in water (4 ml) and filtered to give 5-chloro-3-[(4-amino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone hydrochloride (1.0 g)

mp : 261-263°C

IR (Nujol) : 2740, 2650, 2570, 2070, 1670, 1640, 1590, 1535, 1465, 1350, 1250, 1100, 805 cm^{-1}

NMR (D_2O , δ) : 3.0-3.3 (4H, m), 3.6-4.0 (4H, m), 4.93 (2H, s), 7.0-7.6 (3H, m)

35

Elemental analysis

Calcd. for $C_{13}H_{15}ClN_4O_2S \cdot HCl$:
C 42.98, H 4.44, N 15.42

Found : C 43.14, H 4.68, N 15.54

5

Example 27

To a solution of hydroxylamine hydrochloride (5.48 g) in a mixed solvent of acetonitrile (60 ml) and 6N-hydrochloric acid (30 ml) was added 5-chloro-3-[(4-isobutylideneamino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone (3.0 g). The resulting solution was stirred overnight at room temperature. After stirring for five hours under ice cooling, the crystalline precipitates were filtered, and washed successively with water (6 ml) and methylene chloride (15 ml). This product was further washed by suspending in water (6 ml) and filtered to give 5-chloro-3-[(4-amino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone hydrochloride (1.93 g).

mp : 261-263°C

20 IR (Nujol) : 2740, 2650, 2570, 2070, 1670, 1640, 1590, 1535, 1465, 1350, 1250, 1100, 805 cm^{-1}

NMR (D_2O , δ) : 3.0-3.3 (4H, m), 3.6-4.0 (4H, m), 4.93 (2H, s), 7.0-7.6 (3H, m)

Elemental analysis

25 Calcd. for $C_{13}H_{15}ClN_4O_2S \cdot HCl$:
C 42.98, H 4.44, N 15.42
Found : C 43.14, H 4.68, N 15.54

Example 28

30 In a similar manner to that of Example 25, 26 or 27, there were obtained the following compounds.

(1) 6-Chloro-3-[(4-amino-1-piperazinyl)carbonylmethyl]-2-iminobenzothiazoline

35 mp : 137-142°C (dec.)

IR (Nujol) : 3250, 1655, 1610, 1585, 1240, 1160,
1025, 960, 800 cm^{-1}

5 NMR (CDCl_3 , δ) : 2.58 (4H, t, $J=5\text{Hz}$), 3.64 (4H, t,
J=5Hz), 4.70 (2H, s), 6.75 (1H, d, $J=8\text{Hz}$),
7.10 (1H, dd, $J=2\text{Hz}$, 8Hz), 7.15 (1H, d, $J=2\text{Hz}$)

MASS (m/e) : 325 (M^+), 309 (base), 225

(2) 6-Nitro-3-[(4-amino-1-piperazinyl)carbonylmethyl]-
2-benzothiazolinone hydrochloride

10 mp : 240-242 $^{\circ}\text{C}$

IR (Nujol) : 2700, 2600, 1680, 1650, 1605, 1590,
1515, 1460, 1380, 1340, 1250, 1195, 895 cm^{-1}

15 NMR (DMSO-d_6 , δ) : 2.9-3.9 (8H, m), 5.13 (2H, s),
7.50 (1H, d, $J=9\text{Hz}$), 8.30 (1H, dd, $J=9\text{Hz}$, 3Hz),
8.77 (1H, d, $J=3\text{Hz}$), 9.8 (3H, br s)

(3) 5-Chloro-3-[(4-amino-1-piperazinyl)carbonylmethyl]-
2-benzoxazolinone hydrochloride

20 mp : 240-242 $^{\circ}\text{C}$ (dec.)

IR (Nujol) : 2650, 2600, 1775, 1650, 1600, 1540,
1250, 1030, 935, 810, 690 cm^{-1}

25 NMR (DMSO-d_6 , δ) : 2.8-3.2 (4H, m), 3.5-3.8 (4H, m),
4.90 (2H, s), 7.15 (1H, dd, $J=9\text{Hz}$ and 2Hz),
7.38 (1H, d, $J=9\text{Hz}$), 7.45 (1H, d, $J=2\text{Hz}$),
9.4-10.4 (1H, broad s)

MASS (m/e) : 310 (M^+), 182, 71 (base)

Analysis Calcd. for $\text{C}_{13}\text{H}_{15}\text{ClN}_4\text{O}_3 \cdot \text{HCl}$
C 44.97, H 4.64, N 16.14
Found. : C 44.74, H 4.97, N 16.08

30 (4) 4-Chloro-3-[(4-amino-1-piperazinyl)carbonylmethyl]-
2-benzothiazolinone hydrochloride

mp : 237-251 $^{\circ}\text{C}$ (dec.)

IR (Nujol) : 2760, 2700, 2610, 1665, 1630 cm^{-1}

35 NMR (DMSO-d_6 , δ) : 2.8-3.2 (4H, m), 3.5-3.9 (4H, m),

5.21 (2H, s), 7.18 (1H, dd, J=7.5Hz), 7.38 (1H, dd, J=7.5Hz and 2.0Hz), 7.70 (1H, dd, J=7.5Hz, 2Hz), 9.5-10.3 (3H, broad s)

MASS (m/e) : 326 (M^+), 226, 198 (base), 170, 71

5 Analysis Calcd. for $C_{13}H_{15}ClN_4O_2S \cdot HCl$

C 42.98, H 4.44, N 15.42

Found : C 42.93, H 4.69, N 15.52

(5) 6-Chloro-3-[(4-amino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone hydrochloride

10 mp : 215-243°C (dec.)

IR (Nujol) : 2700, 2600, 1670, 1650 cm^{-1}

15 NMR (DMSO-d₆, δ) : 2.9-3.3 (4H, m), 3.5-3.8 (4H, m), 4.99 (2H, s), 7.25 (1H, d, J=8Hz), 7.42 (1H, dd, J=8Hz and 2Hz), 7.82 (1H, d, J=2Hz), 9.2-10.5 (3H, br s)

MASS (m/e) : 326 (M^+), 198, 170, 71, 36 (base)

20 Analysis Calcd. for $C_{13}H_{15}ClN_4O_2S \cdot HCl \cdot 1/2H_2O$

C 41.94, H 4.60, N 15.05

Found : C 41.75, H 4.46, N 15.19

(6) 7-Chloro-3-[(4-amino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone hydrochloride

25 mp : 233-242°C (dec.)

IR (Nujol) : 2750-2600, 1690, 1670 cm^{-1}

20 NMR (DMSO-d₆, δ) : 2.8-3.2 (4H, m), 3.4-3.8 (4H, m), 5.00 (2H, s), 7.1-7.5 (3H, m), 9.2-9.9 (3H, broad s)

MASS (m/e) : 326 (M^+ , base)

30 Analysis Calcd. for $C_{13}H_{15}ClN_4O_2S \cdot HCl$

C 42.98, H 4.44, N 15.42

Found : C 42.57, H 4.65, N 15.38

(7) 5-Methyl-3-[(4-amino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone hydrochloride

35

mp : 230-240°C (dec.)

IR (Nujol) : 2750, 2670, 2610, 1670, 1645 cm^{-1}

NMR (DMSO-d₆, δ) : 2.34 (3H, s), 2.8-3.2 (4H, m),
3.4-3.8 (4H, m), 4.92 (2H, s), 7.00 (1H, d,
J=7.5Hz), 7.04 (1H, s), 7.49 (1H, d, J=7.5Hz),
9.3-10.3 (3H, broad s)

MASS (m/e) : 306 (M⁺), 206, 178, 150, 71 (base),

Analysis Calcd. for C₁₄H₁₈N₄O₂S·HCl

C 49.05, H 5.59, N 16.34

10 Found : C 49.13, H 5.61, N 16.46

(8) 5-Trifluoromethyl-3-[(4-amino-1-piperazinyl)-
carbonylmethyl]-2-benzothiazolinone hydrochloride

mp : 250-260°C (dec.)

15 IR (Nujol) : 2750, 2670, 1690, 1655 cm^{-1}

NMR (DMSO-d₆, δ) : 2.8-3.2 (4H, m), 3.5-3.8 (4H, m),
5.07 (2H, s), 7.48 (1H, d, J=7.5Hz), 7.60
(1H, s), 7.87 (1H, d, J=7.5Hz), 9.3-9.9 (3H,
broad s)

20 MASS (m/e) : 360 (M⁺), 204, 71 (base)

Analysis Calcd. for C₁₄H₁₅F₃N₄O₂S·HCl·1/2H₂O

C 41.44, H 4.22, N 13.81

Found : C 41.51, H 4.45, N 13.81

25 (9) 5-Chloro-3-[(4-amino-1-homopiperazinyl)carbonyl-
methyl]-2-benzothiazolinone hydrochloride

mp : 228-232°C

IR (Nujol) : 3280, 3160, 2570, 1710, 1660, 1620,
1590, 1180, 1080, 900, 800 cm^{-1}

30 NMR (DMSO-d₆, δ) : 1.8-2.3 (2H, m), 2.9-3.9 (8H,
m), 4.95 (2H, s), 7.25 (1H, dd, J=8Hz and 2Hz),
7.48 (1H, d, J=2Hz), 7.71 (1H, d, J=8Hz),
8.8-10.5 (3H, broad s)

Analysis Calcd. for C₁₄H₁₇ClN₄O₂S·HCl

C 44.57, H 4.81, N 14.85

35 Found : C 44.91, H 4.87, N 14.92

(10) 5-Chloro-3-[(4-amino-3-methyl-1-piperazinyl)-carbonylmethyl]-2-benzothiazolinone hydrochloride
mp : 168-170°C
IR (Nujol) : 3400, 2670, 2600, 1680, 1655 cm^{-1}
5 NMR (DMSO-d₆, 60°C, δ) : 1.22 (3H, d, J=5Hz),
2.7-3.6 (5H, m), 3.8-4.2 (2H, m), 4.94 (2H, s),
7.15 (1H, dd, J=8Hz and 2Hz), 7.33 (1H, d,
J=2Hz), 7.58 (1H, d, J=8Hz), 8.0-10.0 (3H,
broad s)
10 Analysis Calcd. for C₁₄H₁₇ClN₄O₂S·HCl·H₂O
C 42.54, H 5.10, N 14.17
Found : C 42.97, H 5.12, N 13.80

(11) 5-Chloro-6-phenyl-3-[(4-amino-1-piperazinyl)-carbonylmethyl]-2-benzothiazolinone hydrochloride
15 mp : >270°C
IR (Nujol) : 2700, 2600, 1690, 1655, 1600, 1535,
1460, 1260, 1245, 1175, 1075, 990 cm^{-1}
NMR (DMSO-d₆, δ) : 2.9-3.3 (4H, m), 3.6-3.9 (4H,
20 m), 5.07 (2H, s), 7.5-7.8 (7H, m), 9.8 (3H,
br s)

(12) 5-Chloro-6-bromo-3-[(4-amino-1-piperazinyl)-carbonylmethyl]-2-benzothiazolinone hydrochloride
25 mp : 263-265°C (dec.)
IR (Nujol) : 2650, 2600, 1705, 1660, 1590, 1520,
1470, 1380, 1350, 1310, 1240, 1190, 1070,
990 cm^{-1}
NMR (DMSO-d₆, δ) : 2.8-3.3 (4H, m), 3.5-3.9 (4H, m),
30 5.00 (2H, s), 7.70 (1H, s), 8.17 (1H, s),
9.7 (3H, br s)

(13) 6-Chloro-2-oxo-1-[(4-amino-1-piperazinyl)carbonylmethyl]-1,2-dihydrothiazolo[5,4-b]pyridine hydrochloride
35

mp : 238-246°C (dec.)

IR (Nujol) : 2700, 2600, 1690, 1640, 1580, 1535,
1410, 1260, 1200 cm^{-1}

5 NMR (DMSO-d₆, δ) : 3.04 (4H, m), 3.63 (4H, broad s),
5.07 (2H, s), 8.02 (1H, d, J=2Hz), 8.38 (1H,
d, J=2Hz), 9.90 (3H, broad s)

MASS : 327 (M⁺), 227, 199, 171, 71 (Base)

Elemental analysis

Calcd. for C₁₂H₁₄ClN₅O₂S·HCl

10 C 39.57, H 4.15, N 19.23

Found : C 39.82, H 4.02, N 19.38

(14) 3-[(4-Amino-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone hydrochloride

15 mp : 249-258°C (dec.)

IR (Nujol) : 2750, 2700, 2620, 2080, 1670, 1640,
1610, 1545, 1260, 760 cm^{-1}

20 NMR (DMSO-d₆, δ) : 2.8-3.3 (4H, m), 3.3-3.9 (4H, m),
4.95 (2H, s), 7.0-7.5 (3H, m), 7.63 (1H, dd,
J=2Hz and 7.5Hz), 9.0-10.5 (3H, broad s)

Elemental analysis

Calcd. for C₁₃H₁₆N₄O₂S·HCl :

C 47.49, H 5.21, N 17.04

Found : C 47.54, H 5.02, N 17.14

25

Example 29

In a similar manner to that of Example 15,
there were obtained the following compounds.

30 (1) 5-Chloro-3-[(4-benzylideneamino-1-piperazinyl)-carbonylmethyl]-2-benzothiazolinone

mp : 213-215°C

IR (Nujol) : 1700 (sh), 1680, 1650, 1590 cm^{-1}

35 NMR (DMSO-d₆, δ) : 2.87-3.47 (4H, m), 3.47-3.93
(4H, m), 5.00 (2H, s), 7.10-7.87 (9H, m)

(2) 6-Chloro-1-[(4-benzylideneamino-1-piperazinyl)-carbonylmethyl]-2,3-indolinedione
mp : 241-243°C
IR (Nujol) : 1755, 1735, 1665, 1620, 1375, 1255,
5 1130, 1100, 1000 cm^{-1}

(3) 6-Chloro-3-[(4-benzylideneamino-1-piperazinyl)-carbonylmethyl]-2-iminobenzothiazoline
mp : 158-160°C (dec.)
10 IR (Nujol) : 3350, 1625, 1575, 990, 800, 750 cm^{-1}

(4) 5-Chloro-3-[(4-(2-hydroxybenzylideneamino)-1-piperazinyl)carbonylmethyl]-2-benzothiazolinone
mp : 206-207°C
15 IR (Nujol) : 1690, 1660, 1590 cm^{-1}
NMR (DMSO- d_6 , δ) : 3.0-3.5 (4H, m), 3.5-4.1 (4H, m),
5.00 (2H, s), 7.3-7.8 (8H, m), 11.07 (1H, s)

(5) 5-Chloro-3-[(4-isobutyrideneamino-1-piperazinyl)-carbonylmethyl]-2-benzothiazolinone
mp : 147-149°C
20 IR (Nujol) : 1690, 1650, 1590 cm^{-1}
NMR (CDCl₃, δ) : 1.05 (6H, d, J=7Hz), 2.45 (1H, sepl, J=7Hz), 3.00 (4H, m), 3.73 (4H, m),
25 4.70 (2H, s), 6.87-7.43 (4H, m)

(6) 6-Nitro-3-[(4-benzylideneamino-1-piperazinyl)-carbonylmethyl]-2-benzothiazolinone
mp : 248-250°C
30 IR (Nujol) : 1690, 1660, 1460, 1340, 1250, 1140,
990 cm^{-1}

Example 30

35 A mixture of 6-chloro-1-[(4-benzylideneamino-1-piperazinyl)carbonylmethyl]-2,3-indolinedione (1.5 g) and

hydroxylamine hydrochloride (2.5 g) in acetonitrile (100 ml), conc. hydrochloric acid (50 ml), and water (50 ml) was heated at 40°C for 2 hour. The reaction mixture was concentrated up to 20 ml and the precipitates appeared were filtered, and air-dried. This crude material was recrystallized from aqueous methanol at first, and from water finally to give 6-chloro-1-[(4-amino-1-piperazinyl)carbonylmethyl]-3-hydroxyimino-2-indolinone hydrochloride (0.54 g).

10 mp : 209-214°C

IR (Nujol) : 2600, 1715, 1640, 1610, 1380, 1270, 1250, 1200, 1100, 1040, 1025 cm^{-1}

15 NMR (DMSO- d_6 , δ) : 2.8-3.3 (4H, m), 3.4-3.8 (4H, m), 4.77 (2H, s), 7.13 (1H, d, $J=8\text{Hz}$), 7.20 (1H, s), 7.97 (1H, d, $J=8\text{Hz}$)

MASS (m/e) : 337 (M^+), 320 (base peak)

20

25

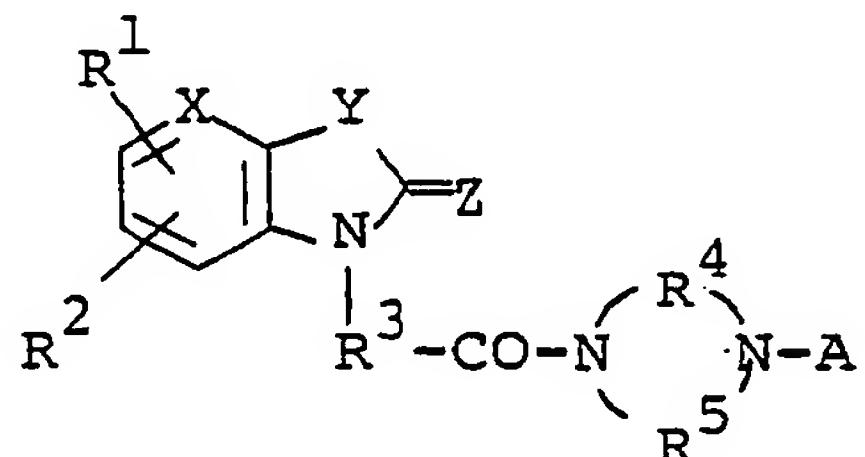
30

35

What we claim is :

1. A compound of the formula :

5



10

wherein R¹ and R² are each hydrogen, halogen, aryl, lower alkyl, halo(lower)alkyl or nitro,

15

R³ is lower alkylene,

R⁴ and R⁵ are each lower alkylene,

X is CH or N,

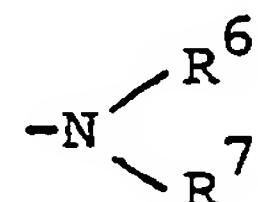
Y is S, O, NH, C=N-OH or CO,

Z is O or NH,

20

and

A is hydrogen, nitroso, amidino, a group of the formula :



25

wherein R⁶ and R⁷ are each hydrogen, lower alkyl, acyl, or lower alkaneimidoyl which may be substituted with esterified carboxy, or

30

a group of the formula : -N=R⁸

wherein R⁸ is lower alkylidene which may be substituted with aryl optionally substituted with suitable substituent(s),

35

and pharmaceutically acceptable salts thereof.

2. A compound of claim 1, wherein Y is S, O, C=N-OH or CO, and A is hydrogen, nitroso, amidino, a group of the formula :



5

wherein R⁶ and R⁷ are each hydrogen, lower alkyl, lower alkanoyl, lower alkoxycarbonyl, lower alkane-sulfonyl, aroyl which may be substituted with halogen, arylcarbamoyl which may be substituted with halogen, or lower alkaneimidoyl which may be substituted with ar(lower)alkoxycarbonyl which may have a nitro group, or a group of the formula : -N=R⁸ wherein R⁸ is lower alkylidene which may be substituted with aryl optionally substituted with hydroxy.

10

3. A compound of claim 2, wherein R¹ and R² are each hydrogen, chlorine, bromine, phenyl, methyl, trifluoromethyl or nitro, R³ is methylene, R⁴ is ethylene or methylethylene, R⁵ is ethylene or trimethylene, and A is hydrogen, nitroso, amidino, a group of the formula : -N=R⁶ wherein R⁶ and R⁷ are each hydrogen, methyl, formyl, acetyl, ethoxycarbonyl, methanesulfonyl, benzoyl which may be substituted with fluorine, phenylcarbamoyl which may be substituted with fluorine, or acetimidoyl which may be substituted with p-nitrobenzyloxycarbonyl, or a group of the formula : -N=R⁸ wherein R⁸ is methylene which may be substituted with phenyl optionally substituted with hydroxy, or isobutylidene.

20

25

30

4. A compound of claim 2, wherein R¹ and R² are each hydrogen or halogen, X is CH, Y is S, Z is O and A is amino.

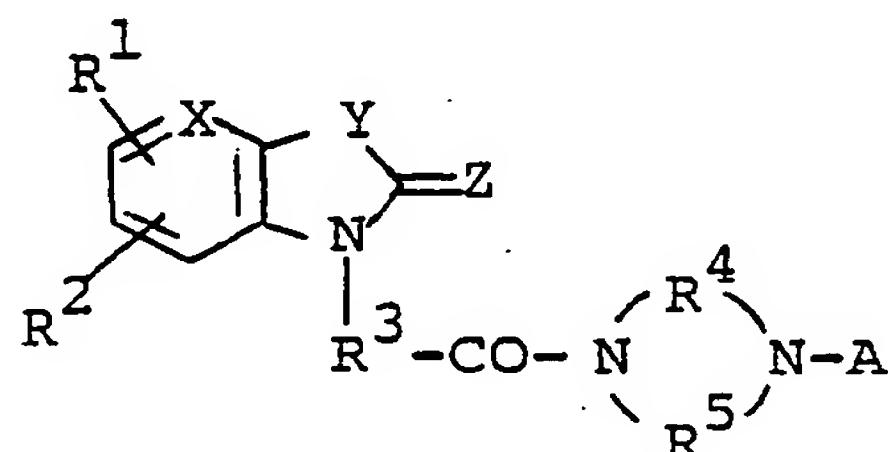
35

5. A compound of claim 4, wherein
R¹ is hydrogen, R² is chlorine, R³ is methylene and
R⁴ and R⁵ are each ethylene.

5 6. A compound of claim 5, which is
5-chloro-3-[(4-amino-1-piperazinyl)carbonylmethyl]-
2-benzothiazolinone or its hydrochloride.

7. A process for preparing a compound of the formula:

10



15

wherein R¹ and R² are each hydrogen, halogen, aryl,
20 lower alkyl, halo(lower)alkyl or nitro,

R³ is lower alkylene,

R⁴ and R⁵ are each lower alkylene,

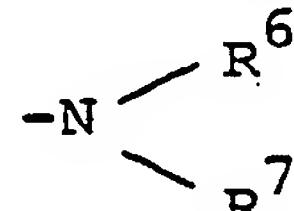
X is CH or N,

Y is S, O, NH, C=N-OH or CO,

Z is O or NH,

25 and

A is hydrogen, nitroso, amidino, a group of
the formula :



30

wherein R⁶ and R⁷ are each hydrogen,
lower alkyl, acyl or lower
alkaneimidoyl which may be
substituted with esterified
carboxy or

35

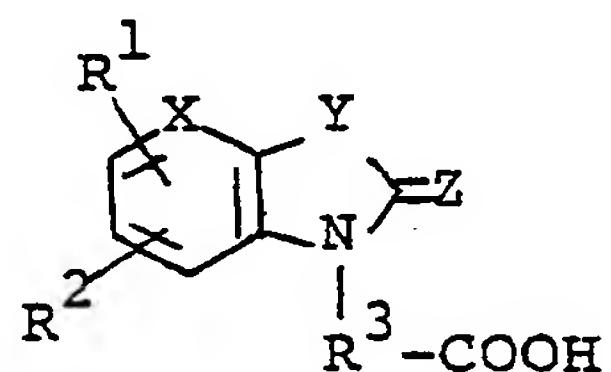
a group of the formula : -N=R⁸

wherein R^8 is lower alkylidene which may be substituted with aryl optionally substituted with suitable substituent(s),

5 or pharmaceutically acceptable salts thereof, which comprises

(1) reacting a compound of the formula :

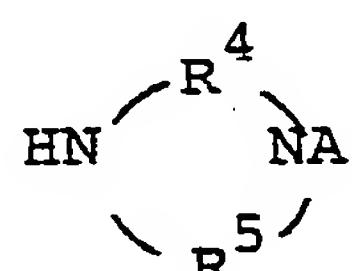
10



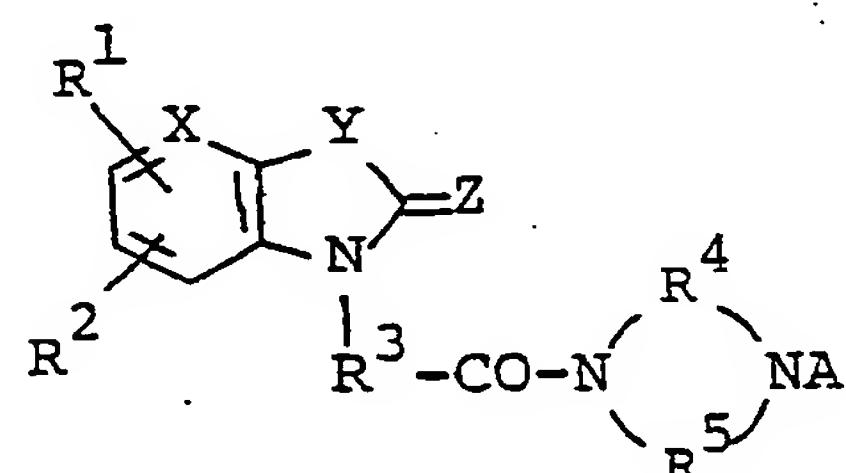
15

or its reactive derivative at the carboxy group or its salt with a compound of the formula :

20



25



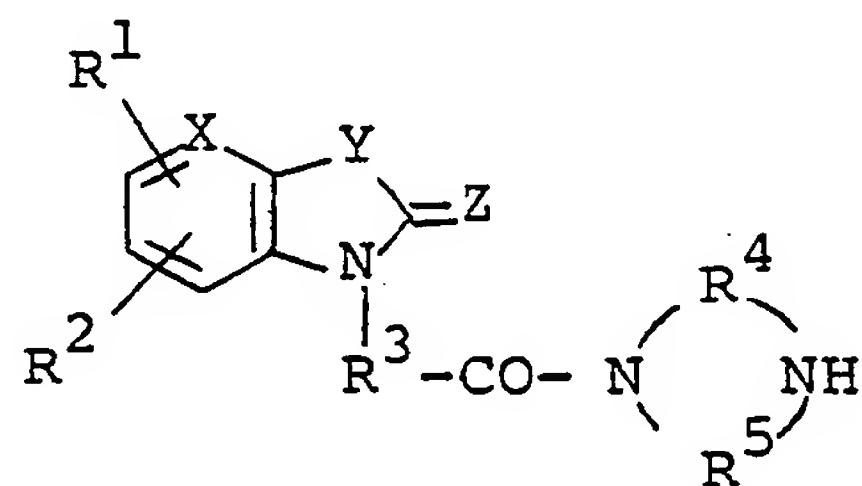
30

or its salt, in which R^1 , R^2 , R^3 , R^4 , R^5 , X , Y , Z and A are each as defined above, or

(2) subjecting a compound of the formula :

35

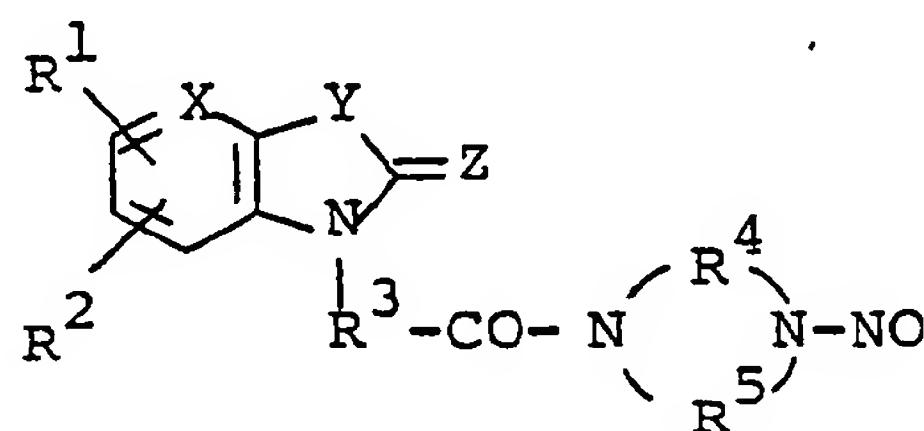
5



10

or its salt to nitrosation reaction to give a compound of the formula :

15

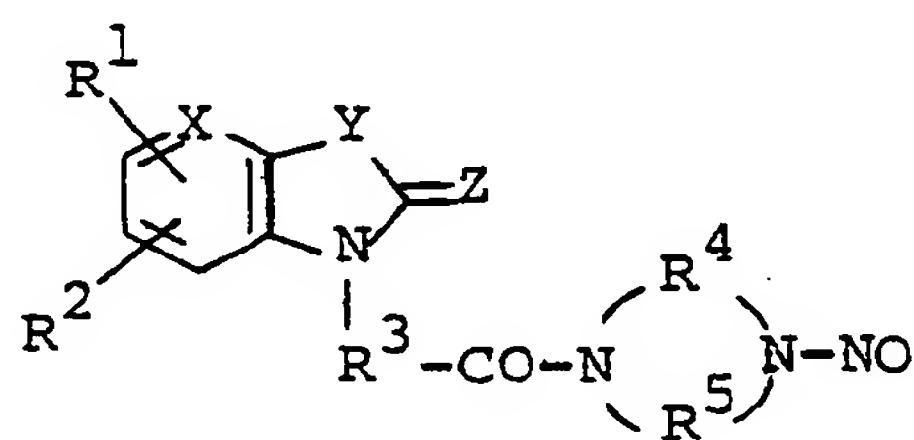


20

or its salt, in which R¹, R², R³, R⁴, R⁵, X, Y and Z are each as defined above, or

(3) reducing a compound of the formula :

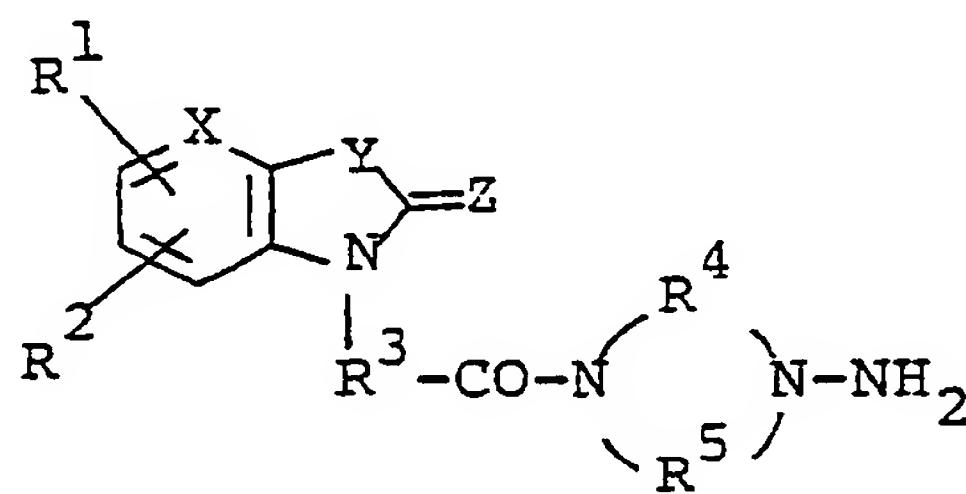
25



30

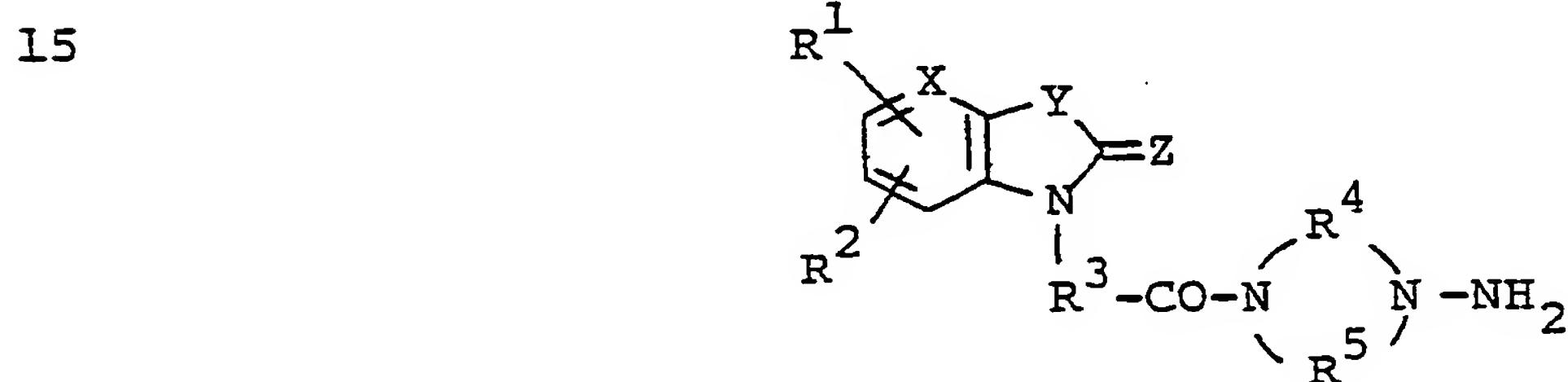
or its salt to give a compound of the formula :

35



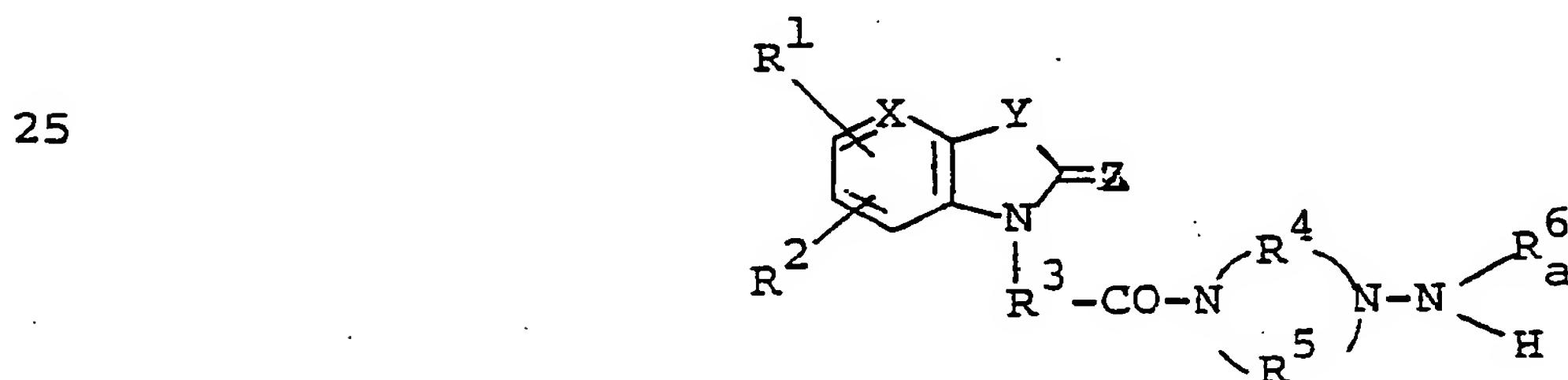
10 or its salt, in which R^1 , R^2 , R^3 , R^4 , R^5 , X , Y and Z are each as defined above,
or

(4) acylating a compound of the formula :



20

or its salt to give a compound of the formula :

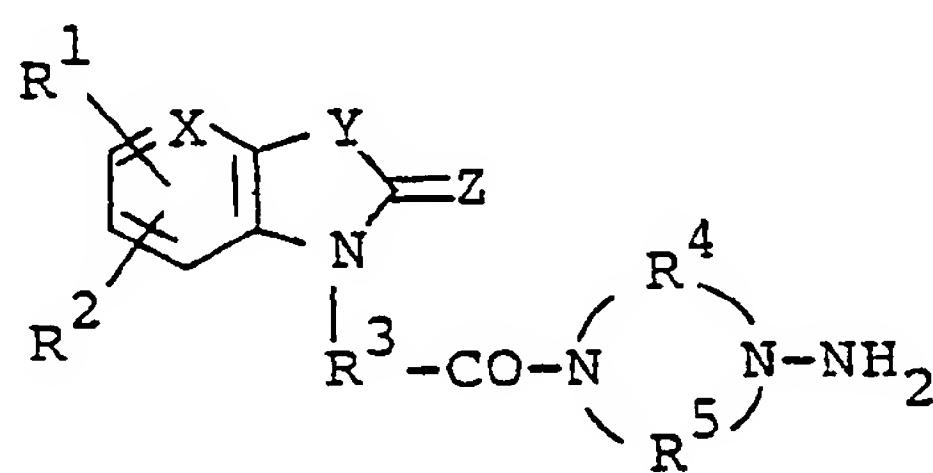


30

or its salt, in which R^1 , R^2 , R^3 , R^4 , R^5 , X , Y and Z are each as defined above and R^6_a is acyl,
or

35 (5) subjecting a compound of the formula :

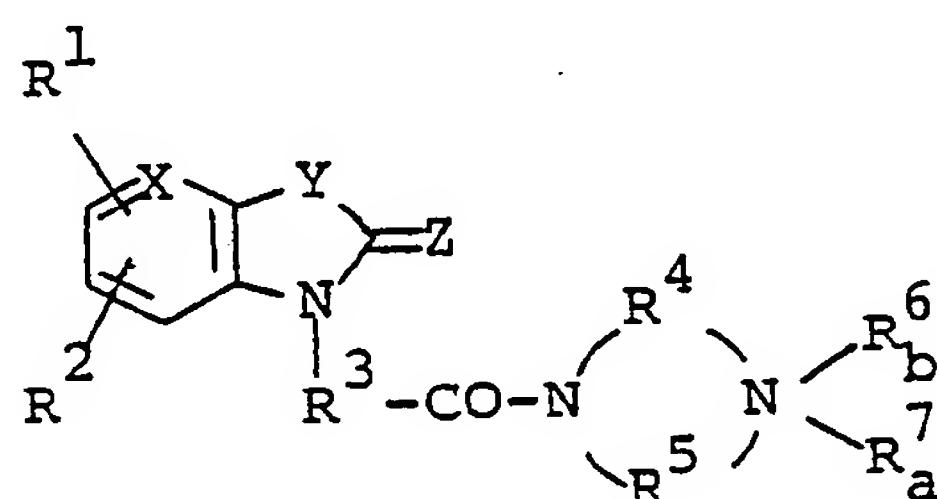
5



10

or its salt to alkylation reaction to give a compound of the formula :

15



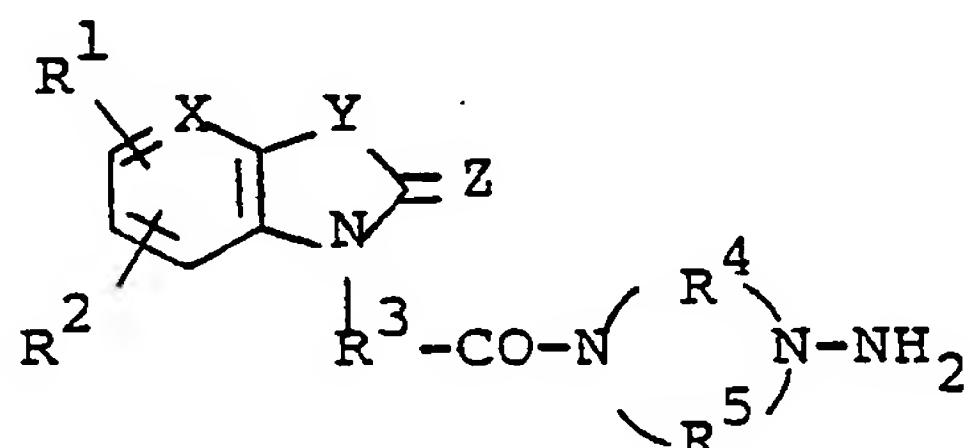
20

or its salt, in which R¹, R², R³, R⁴, R⁵, X, Y and Z are each as defined above, R⁶_b is lower alkyl and R⁷_a is hydrogen or lower alkyl, or

25

(6) reacting a compound of the formula :

30



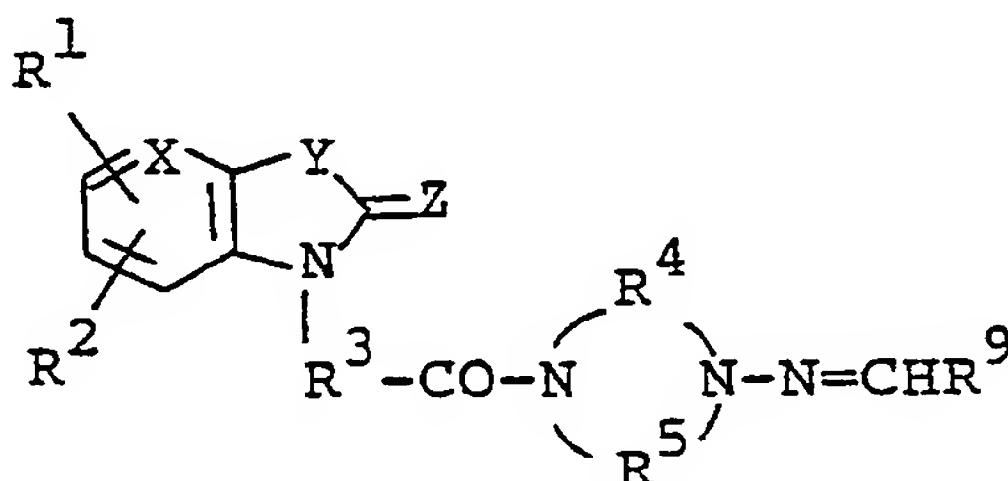
or its salt with a compound of the formula :

35



to give a compound of the formula :

5



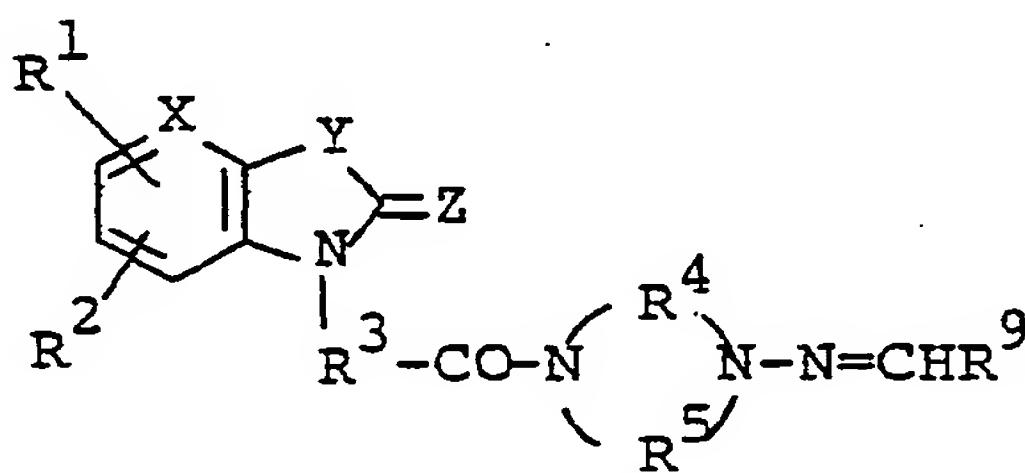
10

or its salt, in which R¹, R², R³, R⁴, R⁵, X, Y and Z are each as defined above, and R⁹ is hydrogen, lower alkyl or aryl optionally substituted with suitable substituent(s), or

15

(7) reducing a compound of the formula :

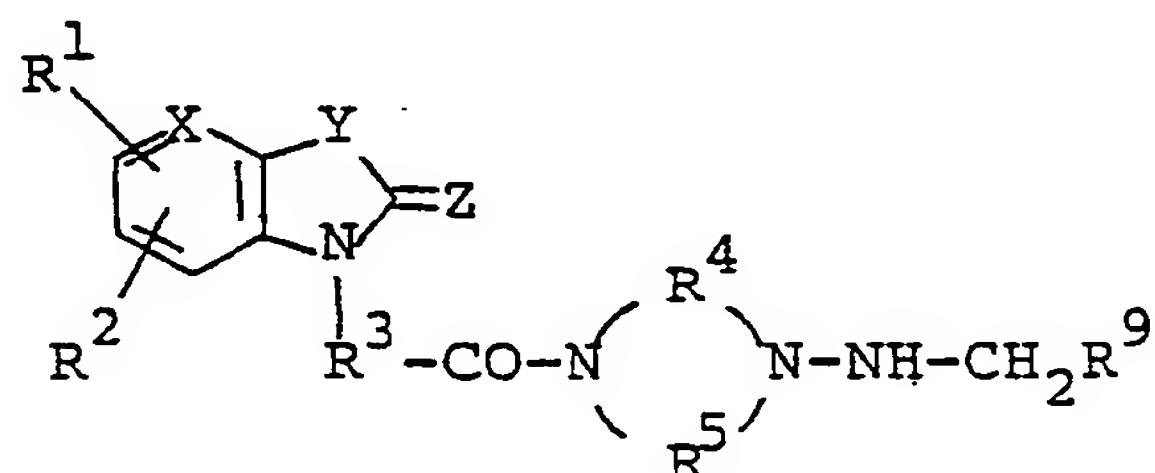
20



25

or its salt to give a compound of the formula :

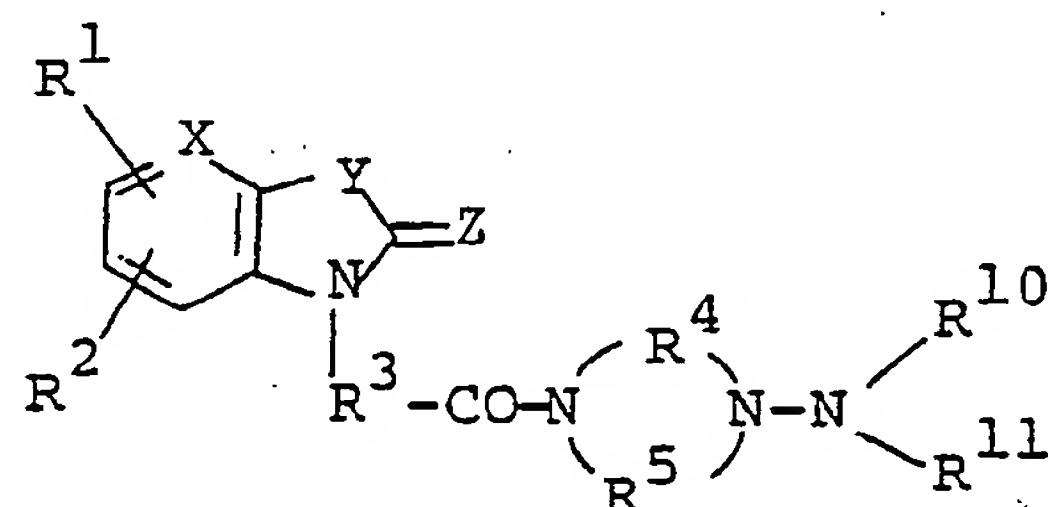
30



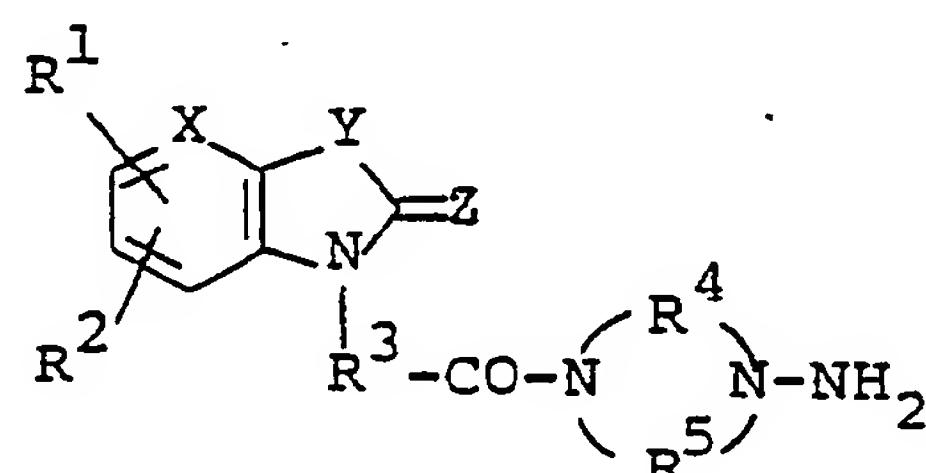
35

or its salt, in which R¹, R², R³, R⁴, R⁵, R⁹, X, Y and Z are each as defined above, or

(8) subjecting a compound of the formula :



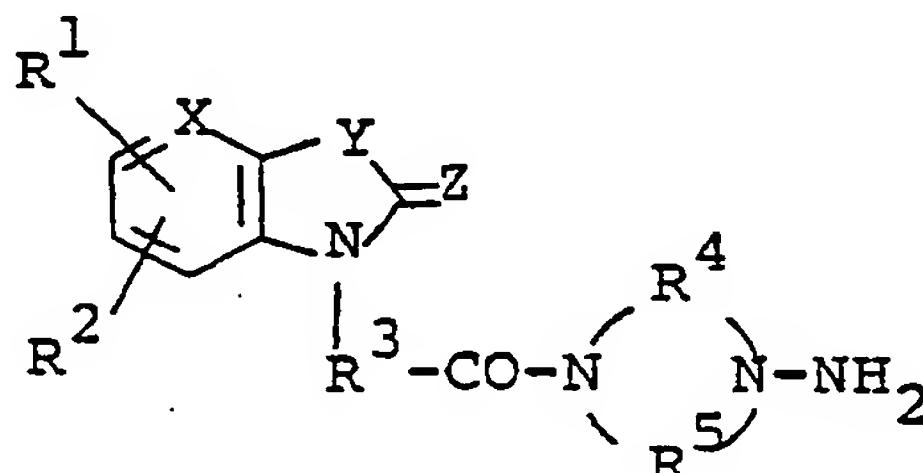
10 or its salt to hydrolysis to give a compound of the formula :



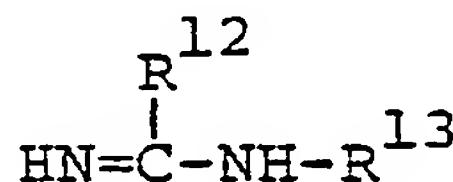
20 or its salt, in which R¹, R², R³, R⁴, R⁵, X, Y and Z are each as defined above, and R¹⁰ is acyl and R¹¹ is hydrogen or R¹⁰ and R¹¹ are combined together to form a group of the formula: =R⁸ where R⁸ is as defined above, or

25

(9) reacting a compound of the formula :

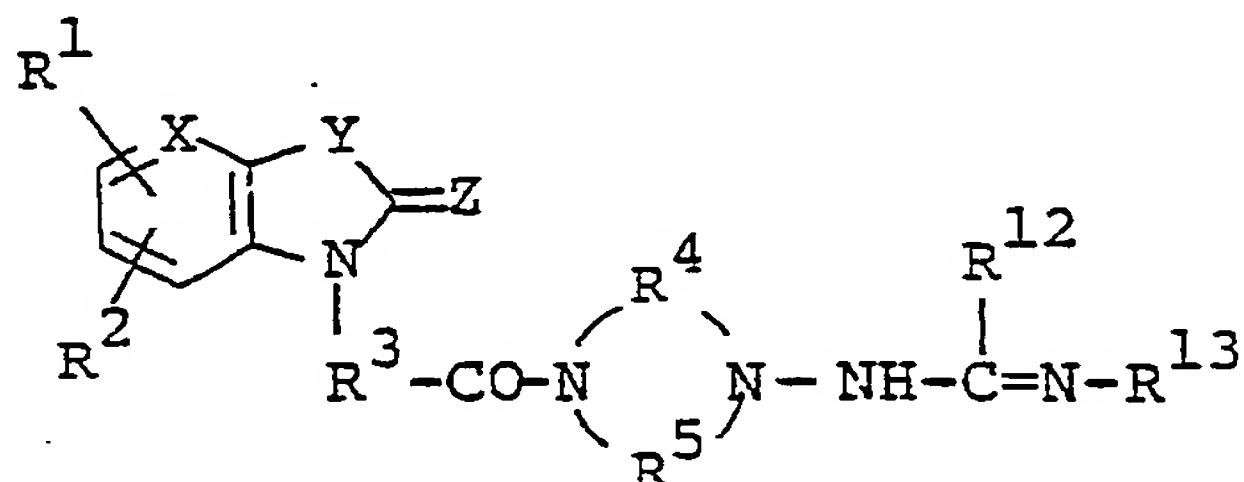


35 or its salt with a compound of the formula :



or its salt to give a compound of the formula:

5



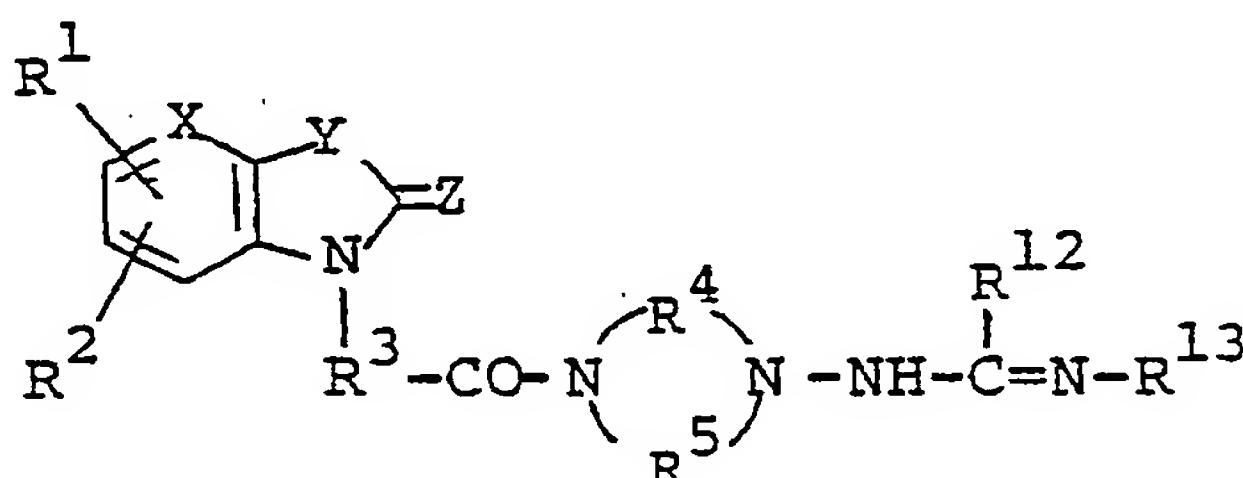
10

or its salt, in which R^1 , R^2 , R^3 , R^4 , R^5 , X , Y and Z are each as defined above, R^{12} is lower alkyl and R^{13} is esterified carboxy, or

15

(10) subjecting a compound of the formula :

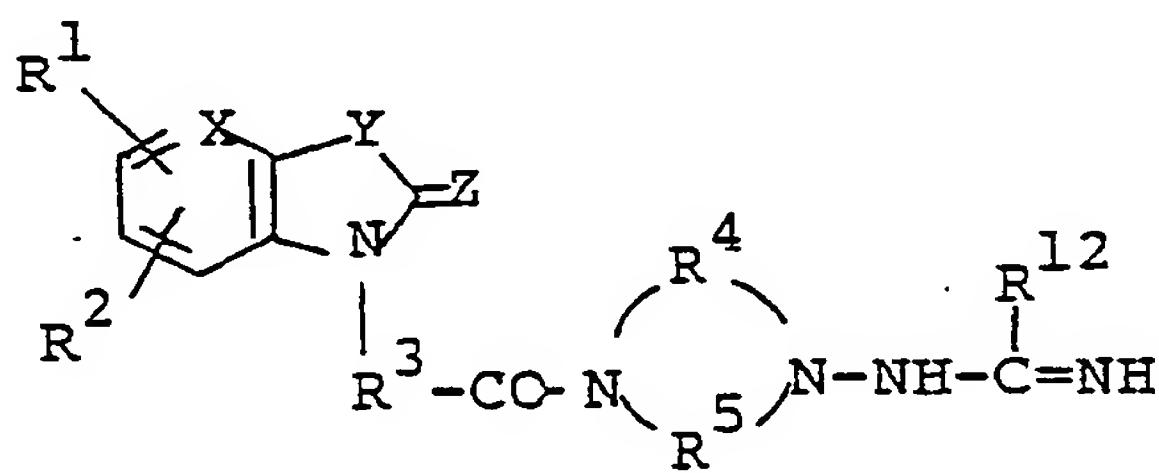
20



25

or its salt to reduction to give a compound of the formula:

30

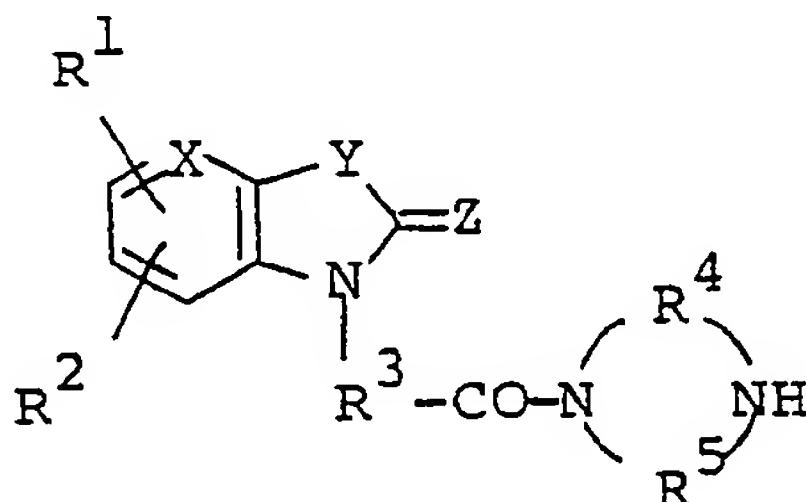


35

or its salt, in which R^1 , R^2 , R^3 , R^4 , R^5 , R^{12} , R^{13} , X , Y and Z are each as defined above,
or

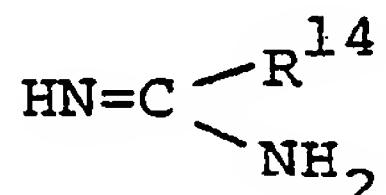
(11) reacting a compound of the formula :

5



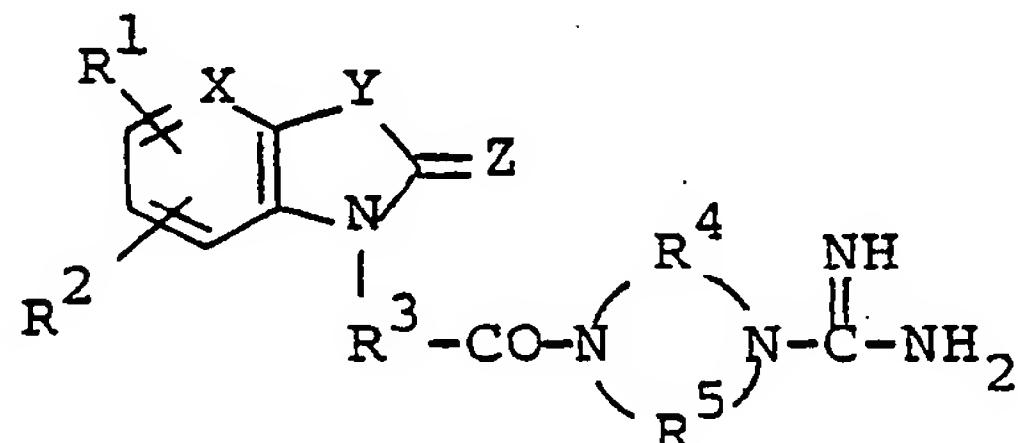
or its salt with a compound of the formula :

10



or its salt to give a compound of the formula :

15



20

or its salt, in which R^1 , R^2 , R^3 , R^4 , R^5 , X , Y and Z are each as defined above, and R^{14} is lower alkylthio.

25

8. A pharmaceutical composition comprising, as an active ingredient, a compound of claim 1 or pharmaceutically acceptable salts thereof in association with pharmaceutically acceptable carrier or excipient.
9. A method for the treatment of thrombosis, inflammation, allergic disease, and pain in human being or animals by administering a compound of claim 1 or pharmaceutically acceptable salts thereof.
- 30 10. A compound of claim 1 for use as a medicament.

35



European Patent
Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention
shall be considered, for the purposes of subsequent
proceedings, as the European search report

0 232 740

EP 87 10 0448

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	GB-A-1 238 673 (FUJISAWA PHARM.) * Claims 1,3-7; pages 1,6-21 * ---	1-3,7, 8,10	C 07 D 277/68 C 07 D 209/38 C 07 D 209/40 C 07 D 263/58
X	US-A-4 279 909 (TOSHIYUTI TAKASHIMA) * Whole document * ---	1-3,8, 10	C 07 D 277/82 C 07 D 417/06 A 61 K 31/495
A	GB-A-1 270 841 (FUJISAWA PHARM.) * Claims, pages 5,6 * ---	1,7,8, 10	C 07 D 513/04/ (C 07 D 513/04 277:00 221:00)
A	CHEMICAL ABSTRACTS, vol. 101. no. 19, November 5, 1984, pages 706-707 ref.no. 171287g; Columbus, Ohio, US & JP-A-59 95 290 (OTSUKA PHARM. FACT., INC.) 01-06-1984 * Abstract * -----	1,8,10	TECHNICAL FIELDS SEARCHED (Int. Cl.4) C 07 D 277/00 C 07 D 209/00 C 07 D 263/00 C 07 D 417/00 C 07 D 513/00

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely: 1-8,10

Claims searched incompletely:

Claims not searched: 9

Reason for the limitation of the search:

Method for treatment of the human or animal body by surgery or therapy (see art. 52(4) of the European Patent Convention).

Place of search	Date of completion of the search	Examiner
The Hague	14-04-1987	HENRY
CATEGORY OF CITED DOCUMENTS		
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		
T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document		